FILE 'HOME' ENTERED AT 09:11:20 ON 12 SEP 2008

=> file reg
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 0.21 | 0.21

FILE 'REGISTRY' ENTERED AT 09:11:43 ON 12 SEP 2008

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STRUCTURE FILE UPDATES: 11 SEP 2008 HIGHEST RN 1048736-36-2
DICTIONARY FILE UPDATES: 11 SEP 2008 HIGHEST RN 1048736-36-2

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TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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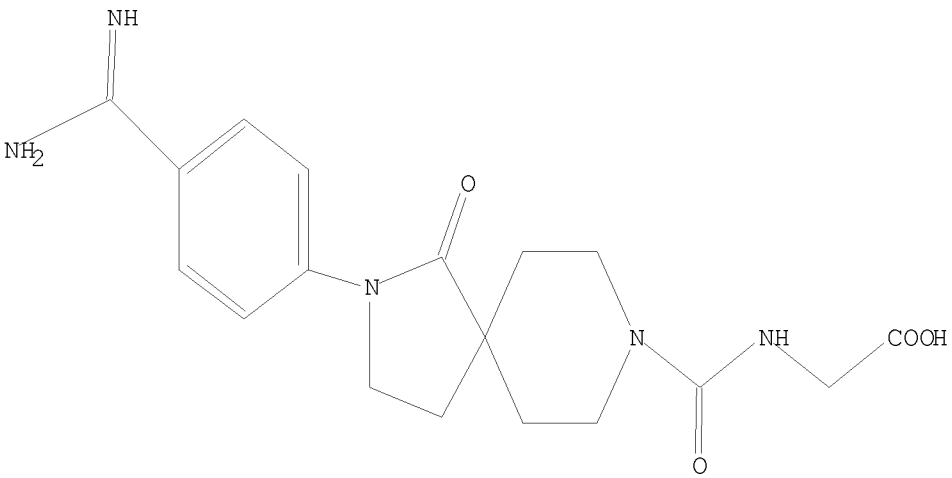
Uploading C:\Program Files\STNEXP\Queries\10564945 str 1.str

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 09:12:13 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        0 TO ITERATE

100.0% PROCESSED        0 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            0 TO        0
PROJECTED ANSWERS:               0 TO        0

L2            0 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 09:12:22 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -        9 TO ITERATE

100.0% PROCESSED        9 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

L3            0 SEA SSS FUL L1

=> s L1 SSS full
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FULL SCREEN SEARCH COMPLETED -        9 TO ITERATE

100.0% PROCESSED        9 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

L4            0 SEA SSS FUL L1

=>
Uploading C:\Program Files\STNEXP\Queries\10564945 str 2.str

L5      STRUCTURE UPLOADED

=> d
L5 HAS NO ANSWERS
L5              STR
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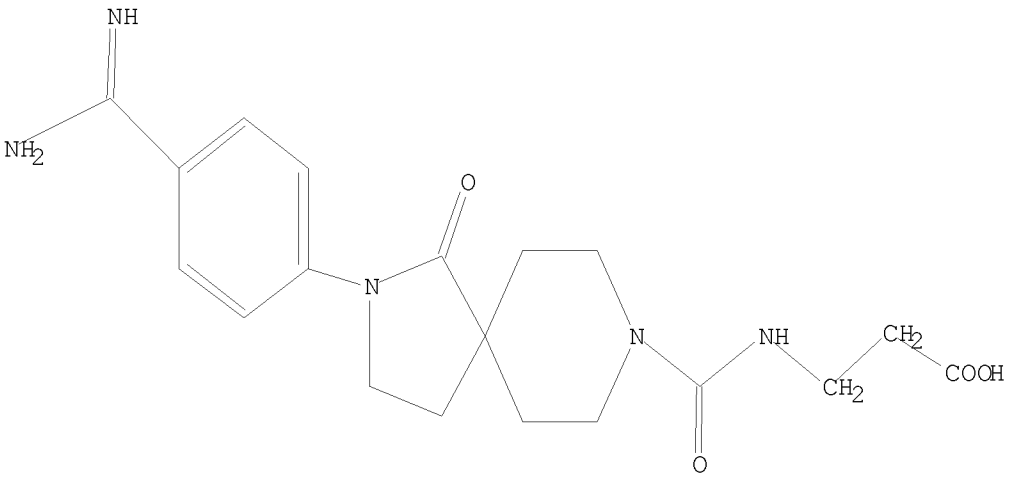

Structure attributes must be viewed using STN Express query preparation.

=> s L2 sss full
FULL SEARCH INITIATED 09:15:47 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 9 TO ITERATE

100.0% PROCESSED 9 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L6 0 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 537.84 538.05

FILE 'CAPLUS' ENTERED AT 09:16:58 ON 12 SEP 2008
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FILE COVERS 1907 - 12 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 11 Sep 2008 (20080911/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2008.

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/legal/infopolicy.html

=> s L5
REG1stRY INITIATED
Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

SAMPLE SEARCH INITIATED 09:17:05 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 3 TO ITERATE

100.0% PROCESSED 3 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

```
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            3 TO      163
PROJECTED ANSWERS:               0 TO        0

L7            0 SEA SSS SAM L5



L8           0 L7

=> ....Testing the current file.... screen

THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE

Please change to a suitable file and repeat your upload

Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       3.84     542.83

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DICTIONARY FILE UPDATES:  11 SEP 2008  HIGHEST RN 1048736-36-2

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predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> ....Testing the current file.... screen

ENTER SCREEN EXPRESSION OR (END):end


=> screen 1006 AND 2076

L9    SCREEN CREATED

=>
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Uploading C:\Program Files\STNEXP\Queries\10564945 str 3.str

L10 STRUCTURE UPLOADED

=> que L10 AND L9

L11 QUE L10 AND L9

=> d L11
L11 HAS NO ANSWERS
L9 SCR 1006 AND 2076
L10 STR

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.
L11 QUE ABB=ON PLU=ON L10 AND L9

=> S L11 SSS full
FULL SEARCH INITIATED 09:24:40 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 45 TO ITERATE

100.0% PROCESSED 45 ITERATIONS 3 ANSWERS
SEARCH TIME: 00.00.01

L12 3 SEA SSS FUL L10 AND L9

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 180.20 723.03

FILE 'CAPLUS' ENTERED AT 09:25:09 ON 12 SEP 2008
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FILE COVERS 1907 - 12 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 11 Sep 2008 (20080911/ED)

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=> s L12

L13 2 L12

=> d L13 1-2 ibib ab

L13 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:429524 CAPLUS
DOCUMENT NUMBER: 142:457060
TITLE: Methods using an activated αIIbβ3 receptor antagonist for treating, preventing, and inhibiting cancer metastasis and tumor formation
INVENTOR(S): Weilbaecher, Katherine; Bakewell, Suzanne
PATENT ASSIGNEE(S): Washington Univ., USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005044978	A2	20050519	WO 2004-US22697	20040715
WO 2005044978	A9	20051103		
WO 2005044978	A3	20060126		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, SZ, BE, CY, FR, GR, IE, IT, MC, NL, SI, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20070185077	A1	20070809	US 2007-564945	20070109
PRIORITY APPLN. INFO.:			US 2003-487325P P	20030715
			WO 2004-US22697 W	20040715

OTHER SOURCE(S): MARPAT 142:457060
AB Methods are disclosed for treating, preventing, or inhibiting tumor cell metastasis, tumor cell formation, and destroying tumors in a subject, comprising administering to the subject in need of such therapy a therapeutically effective amount of an activated αIIbβ3 receptor antagonist and by transplanting affected bone marrow with β3-/- marrow or controlling the expression of β3 integrin in vitro or in vivo. The activated αIIbβ3 receptor antagonist is preferably a spiro compound

L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:196482 CAPLUS
DOCUMENT NUMBER: 140:385509
TITLE: Discovery of Novel 2,8-Diazaspiro[4.5]decanes as Orally Active Glycoprotein IIb-IIIa Antagonists
AUTHOR(S): Mehrotra, Mukund M.; Heath, Julie A.; Smyth, Mark S.; Pandey, Anjali; Rose, Jack W.; Seroogy, Joseph M.; Volkots, Deborah L.; Nannizzi-Alaimo, Lisa; Park, Gary L.; Lambing, Joseph L.; Hollenbach, Stanley J.; Scarborough, Robert M.
CORPORATE SOURCE: Millennium Pharmaceuticals Inc., South San Francisco,

CA, 94080, USA
SOURCE: Journal of Medicinal Chemistry (2004), 47(8), 2037-2061
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:385509

AB In our efforts to develop orally active GPIIb-IIIa antagonists with improved pharmaceutical properties, we have utilized a novel 2,8-diazaspiro[4.5]decane scaffold as a template. We describe here our investigation of a variety of templates including spiropiperidinyl-γ-lactams, spiropiperidinylimide, spiropiperidinylureas, and spiropiperidinylhydantoins. With the appropriate acidic and basic pharmacophores in place, each template yielded analogs with potent GPIIb-IIIa inhibitory activity. One of the compds., 59 (CT50787), was also used to demonstrate for the first time the use of a pharmacol. agent which is αIIbβ3 specific to display biol. activity in a lower species such as mouse and to extend bleeding times. Evaluation of the pharmacokinetic properties of selected compds. from each series in rat, dog, and cynomolgus monkey has led to the identification of 22 (CT51464), a double prodrug, with excellent pharmacokinetic properties. It exhibited good pharmacokinetic profile across species (F% = 33 (Cyno), 73 (dog), 22 (rat); t1/2β = 14.2 h (Cyno), 8.97 h (dog), 1.81 h (rat)). The biol. active form, 23 (CT50728), displayed inhibition of platelet aggregation in platelet rich plasma (PRP) with an IC50 value of 53 nM in citrate buffer, 110 nM in PPACK anticoagulated PRP, and 4 nM in solid-phase GPIIb-IIIa competition binding assay (ELISA). Both 23 and 22 were stable in human liver microsomes, did not inhibit the P 450 3A4 isoenzyme, and had low protein binding (18.22% for 23) and a desirable log P (0.45±0.06 for 22, and -0.91±0.32 for 23). It is predicted that the high oral bioavailability for these compds. in multiple species should translate into lower intra- and intersubject variability in man. The long plasma half-life of the lead is consistent with once or twice daily administration for chronic therapy. Analog 22 (CT51464) thus appears to be a promising oral GPIIb-IIIa inhibitor with significantly improved pharmacokinetic properties over the previously described clin. candidates and may be found useful in the treatment of arterial occlusive disorders.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 09:11:20 ON 12 SEP 2008)

FILE 'REGISTRY' ENTERED AT 09:11:43 ON 12 SEP 2008
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 0 S L1 SSS FULL
L4 0 S L1 SSS FULL
L5 STRUCTURE UPLOADED
L6 0 S L2 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:16:58 ON 12 SEP 2008
S L5

FILE 'REGISTRY' ENTERED AT 09:17:05 ON 12 SEP 2008
L7 0 S L5

FILE 'CAPLUS' ENTERED AT 09:17:05 ON 12 SEP 2008

```
L8            0 S L7

     FILE 'REGISTRY' ENTERED AT 09:22:10 ON 12 SEP 2008
L9              SCREEN 1006 AND 2076
L10             STRUCTURE UPLOADED
L11             QUE L10 AND L9
L12           3 S L11 SSS FULL

     FILE 'CAPLUS' ENTERED AT 09:25:09 ON 12 SEP 2008
L13           2 S L12

=> d l13 1-2 ibib ab hitstr

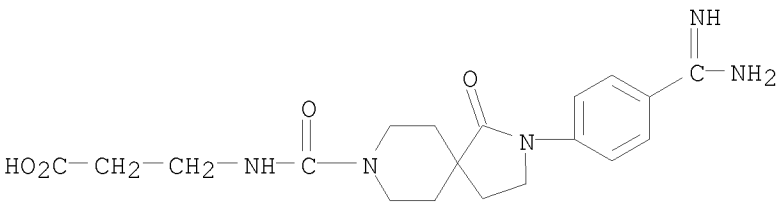
L13  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2005:429524  CAPLUS
DOCUMENT NUMBER:          142:457060
TITLE:                    Methods using an activated αIIbβ3 receptor
                          antagonist for treating, preventing, and inhibiting
                          cancer metastasis and tumor formation
INVENTOR(S):              Weilbaecher, Katherine; Bakewell, Suzanne
PATENT ASSIGNEE(S):       Washington Univ., USA
SOURCE:                   PCT Int. Appl., 81 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     WO 2005044978         A2    20050519    WO 2004-US22697          20040715
     WO 2005044978         A9    20051103
     WO 2005044978         A3    20060126
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW,
             SZ, BE, CY, FR, GR, IE, IT, MC, NL, SI, BF, BJ, CF, CG, CI, CM,
             GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     US 20070185077        A1    20070809    US 2007-564945           20070109
PRIORITY APPLN. INFO.:                     US 2003-487325P     P     20030715
                                           WO 2004-US22697     W     20040715
OTHER SOURCE(S):          MARPAT 142:457060
AB   Methods are disclosed for treating, preventing, or inhibiting tumor cell
     metastasis, tumor cell formation, and destroying tumors in a subject,
     comprising administering to the subject in need of such therapy a
     therapeutically effective amount of an activated αIIbβ3 receptor
     antagonist and by transplanting affected bone marrow with β3-/-
     marrow or controlling the expression of β3 integrin in vitro or in
     vivo.  The activated αIIbβ3 receptor antagonist is preferably a
     spiro compound
IT   685899-12-1, ML 728
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
```

(activated αIIbβ3 receptor antagonist for treating, preventing, and inhibiting cancer metastasis and tumor formation)

RN 685899-12-1 CAPLUS

CN β-Alanine, N-[[2-[4-(aminoiminomethyl)phenyl]-1-oxo-2,8-diazaspiro[4.5]dec-8-yl]carbonyl]- (CA INDEX NAME)



L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:196482 CAPLUS

DOCUMENT NUMBER: 140:385509

TITLE: Discovery of Novel 2,8-Diazaspiro[4.5]decanes as Orally Active Glycoprotein IIb-IIIa Antagonists

AUTHOR(S): Mehrotra, Mukund M.; Heath, Julie A.; Smyth, Mark S.; Pandey, Anjali; Rose, Jack W.; Seroogy, Joseph M.; Volkots, Deborah L.; Nannizzi-Alaimo, Lisa; Park, Gary L.; Lambing, Joseph L.; Hollenbach, Stanley J.; Scarborough, Robert M.

CORPORATE SOURCE: Millennium Pharmaceuticals Inc., South San Francisco, CA, 94080, USA

SOURCE: Journal of Medicinal Chemistry (2004), 47(8), 2037-2061
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 140:385509

AB In our efforts to develop orally active GPIIb-IIIa antagonists with improved pharmaceutical properties, we have utilized a novel 2,8-diazaspiro[4.5]decane scaffold as a template. We describe here our investigation of a variety of templates including spiropiperidinyl-γ-lactams, spiropiperidinylimide, spiropiperidinylureas, and spiropiperidinylhydantoins. With the appropriate acidic and basic pharmacophores in place, each template yielded analogs with potent GPIIb-IIIa inhibitory activity. One of the compds., 59 (CT50787), was also used to demonstrate for the first time the use of a pharmacol. agent which is αIIbβ3 specific to display biol. activity in a lower species such as mouse and to extend bleeding times. Evaluation of the pharmacokinetic properties of selected compds. from each series in rat, dog, and cynomolgus monkey has led to the identification of 22 (CT51464), a double prodrug, with excellent pharmacokinetic properties. It exhibited good pharmacokinetic profile across species (F% = 33 (Cyno), 73 (dog), 22 (rat); t1/2β = 14.2 h (Cyno), 8.97 h (dog), 1.81 h (rat)). The biol. active form, 23 (CT50728), displayed inhibition of platelet aggregation in platelet rich plasma (PRP) with an IC50 value of 53 nM in citrate buffer, 110 nM in PPACK anticoagulated PRP, and 4 nM in solid-phase GPIIb-IIIa competition binding assay (ELISA). Both 23 and 22 were stable in human liver microsomes, did not inhibit the P 450 3A4 isoenzyme, and had low protein binding (18.22% for 23) and a desirable log P (0.45±0.06 for 22, and -0.91±0.32 for 23). It is predicted that the high oral bioavailability for these compds. in multiple species should translate into lower intra- and intersubject variability in man. The long plasma

half-life of the lead is consistent with once or twice daily administration for chronic therapy. Analog 22 (CT51464) thus appears to be a promising oral GPIIb-IIIa inhibitor with significantly improved pharmacokinetic properties over the previously described clin. candidates and may be found useful in the treatment of arterial occlusive disorders.

IT 685899-12-1P, CT 50728
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and structure activity relationships of diazaspirodecanes as glycoprotein IIb-IIIa antagonists)

RN 685899-12-1 CAPLUS

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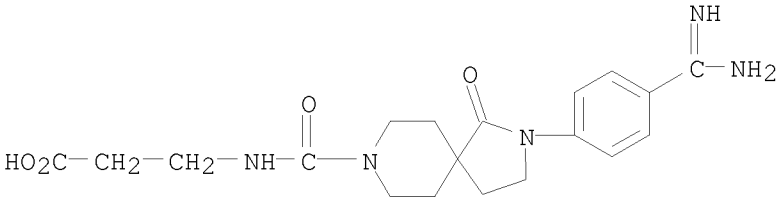
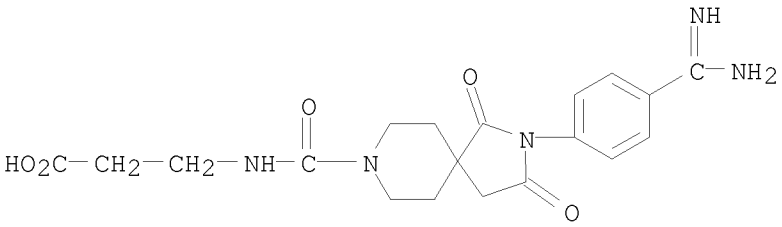


IT 685544-90-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and structure activity relationships of diazaspirodecanes as glycoprotein IIb-IIIa antagonists)

RN 685544-90-5 CAPLUS

CN β-Alanine, N-[[2-[4-(aminoiminomethyl)phenyl]-1,3-dioxo-2,8-diazaspiro[4.5]dec-8-yl]carbonyl]- (CA INDEX NAME)



IT 685899-13-2P, CT 51463
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and structure activity relationships of diazaspirodecanes as glycoprotein IIb-IIIa antagonists)

RN 685899-13-2 CAPLUS

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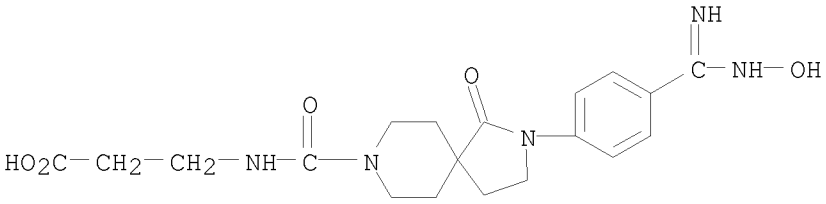

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	18.64	741.67

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.20	-3.20

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LAST RELOADED: Sep 5, 2008 (20080905/UP).

=>
=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.56	743.23

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-3.20

FILE 'CAPLUS' ENTERED AT 09:43:05 ON 12 SEP 2008
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FILE COVERS 1907 - 12 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 11 Sep 2008 (20080911/ED)

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They are available for your review at:

http://www.cas.org/legal/infopolicy.html

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=> s integrins
L14      36123 INTEGRINS

=> s l14 and inhibitors
        583578 INHIBITORS
L15       5292 L14 AND INHIBITORS

=> s l15 and beta-3
       1557088 BETA
           239 BETAS
       1557159 BETA
                  (BETA OR BETAS)
       7372206 3
         29967 BETA-3
                  (BETA(W)3)
L16       2727 L15 AND BETA-3

=> s l16 and alpha-IIb
       1792860 ALPHA
           469 ALPHAS
       1792962 ALPHA
                  (ALPHA OR ALPHAS)
         28443 IIB
             5 IIBS
         28448 IIB
                  (IIB OR IIBS)
          5490 ALPHA-IIB
                  (ALPHA(W)IIB)
L17       1901 L16 AND ALPHA-IIB

=> S L17 AND PY<=2003
      24009633 PY<=2003
L18       1264 L17 AND PY<=2003

=> s L18 and spiro
         26150 SPIRO
            20 SPIROS
         26167 SPIRO
                  (SPIRO OR SPIROS)
L19          4 L18 AND SPIRO

=> d L19 1-4 ibib ab

L19  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2002:211241  CAPLUS
DOCUMENT NUMBER:         137:201219
TITLE:                   Spirocyclic nonpeptide glycoprotein IIb-IIIa
                         antagonists. Part 3: synthesis and SAR of potent and
                         specific 2,8-diazaspiro[4.5]decanes
AUTHOR(S):               Mehrotra, Mukund M.; Heath, Julie A.; Rose, Jack W.;
                         Smyth, Mark S.; Seroogy, Joseph; Volkots, Deborah L.;
                         Ruhter, Gerd; Schotten, Theo; Alaimo, Lisa; Park,
                         Gary; Pandey, Anjali; Scarborough, Robert M.
CORPORATE SOURCE:        Departments of Medicinal Chemistry and Biology, COR
                         Therapeutics Inc., South San Francisco, CA, 94080, USA
SOURCE:                  Bioorganic & Medicinal Chemistry Letters (2002
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), 12(7), 1103-1107
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:201219
AB Pyridinyl substituted 2,8-diazaspiro[4.5]decanes, e.g. I (X, Y = CH, N; n = 0-2; R = HOCOCH2, HOCOCH2O, etc.) and II (Z = O, H2), were synthesized and showed a specific biol. activity as glycoprotein IIb-IIIa antagonists. The potent activity of these diazaspirodecanes as platelet aggregation inhibitors demonstrated the utility of the spiro structures as central templates for nonpeptide RGD (arginine-glycine-aspartic acid) mimics. However, the most potent inhibitor I (X = N, Y = CH, n = 1, R = HOCOCH2CO) showed only marginal oral bioavailability.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:923795 CAPLUS
DOCUMENT NUMBER: 136:53749
TITLE: Preparation of heteroarylalkanoic acids as integrin receptor antagonists
INVENTOR(S): Nagarajan, Scrinivasan Raj; Khanna, Ish Kumar; Tollefson, Michael B.; Mohler, Scott B.; Chen, Barbara; Russell, Mark; Devadas, Balekudru; Penning, Thomas D.; Schretzman, Lori A.; Spangler, Dale P.; Boys, Mark Laurence; Chandrakumar, Nizal Samuel; Lu, Hwang-Fun
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 368 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096334	A2	20011220	WO 2001-US19375	20010615 <--
WO 2001096334	A3	20020912		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 20020133023	A1	20020919	US 2001-881913	20010615 <--
US 6933304	B2	20050823		
EP 1289983	A2	20030312	EP 2001-948424	20010615 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004511434	T	20040415	JP 2002-510476	20010615
US 20040092497	A1	20040513	US 2003-311385	20030905
US 7119098	B2	20061010		

PRIORITY APPLN. INFO.:
US 2000-211781P P 20000615
US 2000-211782P P 20000615
WO 2001-US19375 W 20010615
OTHER SOURCE(S): MARPAT 136:53749

AB Title compds. A1Z2Z1AXYY5(Y3)(Y4)CH2CORb [I; wherein ring A = (un)substituted 4-8 membered monocyclic or 7-12 membered bicyclic ring containing 1-4 heteroatoms, selected from O, N, or S; A1 = (un)substituted 5-9 membered monocyclic or 7-14 membered polycyclic heterocycle containing at least 1 N and optionally 1-4 heteroatoms or groups selected from O, N, S, SO2, or CO; Z1 = CH2, O, CH2O, NH, CO, S, SO, CH(OH), and SO2; Z2 = (un)substituted 1-5 C linker optionally containing 1 or more heteroatoms selected from O, S, and N; Z1Z2 may contain a carboxamide, sulfone, sulfonamide, alkenyl, alkynyl, acyl, or (un)substituted 5- or 6-membered (hetero)aryl; X = CHRe, NRf, O, S, SO2, or CO; Re = H, (cyclo)alkyl, alkoxy(alkyl), OH, alkynyl, alkenyl, haloalkyl, thioalkyl, or aryl; Rf = H, (halo)alkyl, aryl, or benzyl; Y = (CH2)p, CHRg, NRg, CO, or SO2; Rg = H, (halo)alkyl, alkoxyalkyl, alkynyl, (hetero)aryl, OH, alkoxy, or carboxyalkyl; p = 0-1; XY may contain acyl, alkyl, sulfonyl, amino, (thio)ether, carboxamido, sulfonamido, aminosulfonyl, or olefin; Y3 and Y4 = independently H, (halo)alkyl, halo, (hetero)aryl, hydroxyalkyl, alkynyl, etc.; Rb = X2Rh; X2 = O, S, or NRj; Rh and Rj = independently H, (ar)alkyl, acyl, or alkoxyalkyl; with provisos] and their pharmaceutically acceptable salts were prepared for selectively antagonizing the αv. beta.3 and/or the αvβ5 integrin without significantly antagonizing the fibrinogen IIb/IIIa integrin. For example, 3-(hydroxymethyl)benzonitrile was protected with 3,4-dihydro-2H-pyran (89%) and treated with HONH2•HCl to give the benzenecarboximidamide (98%). Cyclization with 3-methylglutaric anhydride in the presence of MeI (64%) and deprotection (98%) gave the Me 1,2,4-oxadiazolebutanoate (64%). Oxidation to the aldehyde, followed by reductive addition of 2-aminopyridine and workup, afforded the oxadiazolebutanoic acid (II). In vitronectin adhesion assays, I antagonized the αv. beta.3 integrin and the αvβ5 integrin with IC50 values of 0.1 nM to 100 μM and < 50 μM, resp. I are useful for the treatment of tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atherosclerosis, macular degeneration, retinopathy, and arthritis (no data).

L19 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:330828 CAPLUS
DOCUMENT NUMBER: 135:152706
TITLE: Spirocyclic non-peptide glycoprotein IIb-IIIa antagonists. Part 2: design of potent antagonists containing the 3-azaspiro[5.5]undec-9-yl template
AUTHOR(S): Pandey, A.; Seroogy, J.; Volkots, D.; Smyth, M. S.; Rose, J.; Mehrotra, M. M.; Heath, J.; Ruhter, G.; Schotten, T.; Scarborough, R. M.
CORPORATE SOURCE: Department of Medicinal Chemistry and Biology, COR Therapeutics, Inc., South San Francisco, CA, 94080, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), 11(10), 1293-1296
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:152706
AB The synthesis and biol. activity of novel glycoprotein IIb-IIIa antagonists containing 3-azaspiro[5.5]undec-9-yl nucleus, e.g. I (R = H, PhCH2OCO, MeC6H4SO2, BuSO2, BuOCO, etc.), were described. The potent activity of these compds. as platelet aggregation inhibitors demonstrated the utility of the monoazaspirocyclic structure as central template for non-peptide RGD mimics.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:398915 CAPLUS
DOCUMENT NUMBER: 125:137093
ORIGINAL REFERENCE NO.: 125:25553a,25556a
TITLE: Non-Peptide glycoprotein IIb/IIIa inhibitors . 9. Centrally constrained alpha-sulfonamides are useful tools for exploring platelet receptor function
AUTHOR(S): Egbertson, M. S.; Bednar, B.; Bednar, R. A.; Hartman, G. D.; Gould, R. J.; Lynch, R. J.; Vassallo, L. M.; Young, S. D.
CORPORATE SOURCE: Dept. Medicinal Chem., Merck Res. Laboratories, West Point, PA, 19486, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(12), 1415-1420
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two fluorescent, centrally constrained fibrinogen receptor antagonists were prepared to probe ligand receptor interactions. The use of these centrally constrained fibrinogen receptor antagonists to characterize the binding affinity of nonfluorescent antagonists to inactive isolated GPIIb/IIIa and GPIIb/IIIa on platelets is described.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	30.04	773.27

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.20	-6.40

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Sep 5, 2008 (20080905/UP).

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=> d his

(FILE 'HOME' ENTERED AT 09:11:20 ON 12 SEP 2008)

FILE 'REGISTRY' ENTERED AT 09:11:43 ON 12 SEP 2008
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 0 S L1 SSS FULL
L4 0 S L1 SSS FULL
L5 STRUCTURE UPLOADED
L6 0 S L2 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:16:58 ON 12 SEP 2008
S L5

FILE 'REGISTRY' ENTERED AT 09:17:05 ON 12 SEP 2008

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L7            0 S L5

     FILE 'CAPLUS' ENTERED AT 09:17:05 ON 12 SEP 2008
L8            0 S L7

     FILE 'REGISTRY' ENTERED AT 09:22:10 ON 12 SEP 2008
L9              SCREEN 1006 AND 2076
L10             STRUCTURE UPLOADED
L11             QUE L10 AND L9
L12           3 S L11 SSS FULL

     FILE 'CAPLUS' ENTERED AT 09:25:09 ON 12 SEP 2008
L13           2 S L12

     FILE 'STNGUIDE' ENTERED AT 09:27:23 ON 12 SEP 2008

     FILE 'CAPLUS' ENTERED AT 09:43:05 ON 12 SEP 2008
L14       36123 S INTEGRINS
L15        5292 S L14 AND INHIBITORS
L16        2727 S L15 AND BETA-3
L17        1901 S L16 AND ALPHA-IIB
L18        1264 S L17 AND PY<=2003
L19           4 S L18 AND SPIRO

     FILE 'STNGUIDE' ENTERED AT 09:44:50 ON 12 SEP 2008

=> L18 and "integrin receptor"
L18 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s L18 and "integrin receptor"
'2003' NOT A VALID FIELD CODE
             0 INTEGRINS
             0 INHIBITORS
             0 BETA
           182 3
             0 BETA-3
                 (BETA(W)3)
             0 ALPHA
             0 IIB
             0 ALPHA-IIB
                 (ALPHA(W)IIB)
             0 PY<=2003
             0 "INTEGRIN"
             0 "RECEPTOR"
             0 "INTEGRIN RECEPTOR"
                 ("INTEGRIN"(W)"RECEPTOR")
L20          0 L18 AND "INTEGRIN RECEPTOR"

=> file caplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   2.94     776.21

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                   0.00      -6.40

FILE 'CAPLUS' ENTERED AT 10:14:04 ON 12 SEP 2008
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FILE COVERS 1907 - 12 Sep 2008 VOL 149 ISS 12
FILE LAST UPDATED: 11 Sep 2008 (20080911/ED)

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reclassification data for the second quarter of 2008.

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http://www.cas.org/legal/infopolicy.html

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=> s L18 and "integrin receptor"
         27008 "INTEGRIN"
         36123 "INTEGRINS"
         42406 "INTEGRIN"
                 ("INTEGRIN" OR "INTEGRINS")
        769708 "RECEPTOR"
        708570 "RECEPTORS"
        920558 "RECEPTOR"
                 ("RECEPTOR" OR "RECEPTORS")
          2513 "INTEGRIN RECEPTOR"
                 ("INTEGRIN"(W)"RECEPTOR")
L21         46 L18 AND "INTEGRIN RECEPTOR"

=> s l21 and beta-3
       1557088 BETA
           239 BETAS
       1557159 BETA
                 (BETA OR BETAS)
       7372206 3
         29967 BETA-3
                 (BETA(W)3)
L22         46 L21 AND BETA-3

=> s L22 and bone
        234312 BONE
         24682 BONES
        241235 BONE
                 (BONE OR BONES)
L23          5 L22 AND BONE

=> d L23 1-5 ibib ab

L23  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:282116  CAPLUS
DOCUMENT NUMBER:         138:304291
```

TITLE: New benzoxazine derivatives useful as αv. beta.3 integrin receptor antagonists
INVENTOR(S): Vianello, Paola; Bandiera, Tiziano; Varasi, Mario
PATENT ASSIGNEE(S): Pharmacia & Upjohn, S.P.A., Italy
SOURCE: U.S. Pat. Appl. Publ., 37 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20030069236	A1	20030410	US 2001-924732	20010808 <--
US 6794385	B2	20040921		

PRIORITY APPLN. INFO.: US 2001-924732 20010808
OTHER SOURCE(S): MARPAT 138:304291

AB The invention relates to a class of compds. I, or pharmaceutically acceptable salts, prodrugs, or esters thereof [wherein: G = Q'NHCONH-, certain cyclic amidines and guanidines, such as pyridin-2-ylamino or imidazolin-2-ylamino, optionally substituted by C1-4-alkyl; Q = NH or O; Q' = H, C1-6 alkyl, Ph, or phenyl-C1-4-alkyl; B = C1-4 alkyl or C2-4 alkenyl; A = CH2, O, S(O)0-2, NH, CONH, CON(Me), NHCO, N(Me)CO; R1 = H, C1-4 alkyl, C1-4 alkoxy, OH, halo, or CF3; X = bond, CO; R2 = H, C1-4 alkyl, C3-7 cycloalkyl, C1-4-alkylcycloalkyl; aryl (substituted by 0-3 of: halo, CF3, C1-4 alkyl, OH and C1-4 alkoxy), aralkyl, and C5-7 monocyclic heteroaryl with 1-3 N/O/S atoms (substituted by 0-3 of: halo, CF3, C1-4 alkyl, OH, and C1-4 alkoxy); Y = (CH2)1-2; R = H, C1-6 alkyl, C2-4 alkenyl, C2-4 alkynyl, aryl, or aryl-C1-4 alkyl; provided that X ≠ bond when G = H2NCONH-]. The invention also relates to pharmaceutical compns. comprising I, and to methods of selectively inhibiting or antagonizing αv. beta.3 integrin using I. The compds. can be used for treatment of a variety of medical conditions, including cancer, and can be used or formulated in combination with other classes of antitumor agents. Approx. 50 compds. are specifically claimed, and synthetic details are given for 6 of them. For example, cyclocondensation of 4-nitro-2-aminophenol with Me 4-bromocrotonate using NaHCO3 in MeOH gave 91% Me (6-nitro-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetate. This compound underwent a sequence of: (1) N-phenylation using 1,4-cyclohexanedione and p-MeC6H4SO3H (25%), (2) hydrogenation of nitro to amino (56%), (3) amidation of amino with N-(benzyloxycarbonyl)-N-(1-oxido-2-pyridinyl)-β-alanine (76%), (4) reduction of the N-oxide using SnCl2 and TiCl4 (99%), (5) reductive removal of benzyloxycarbonyl (79.5%), and (6) saponification of the Me ester with aqueous NaOH in EtOH (35%), to give title compound II [m = 1].. Three standard formulations of the similarly prepared II [m = 2] are described. I [m = 2] bound to human αv. beta. 3 receptor in vitro with an IC50 of 0.024 μM, and to human . alpha.IIb.beta.3 receptor with an IC50 of 27 μM, thus giving a high selectivity ratio of approx. 1000 for αv. beta.3.

L23 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:793620 CAPLUS
DOCUMENT NUMBER: 137:294975
TITLE: Preparation of quinazolinepropanoic acids and related compounds for the treatment of integrin-mediated disorders
INVENTOR(S): Hoekstra, William J.; Lawson, Edward C.; Costanzo,

Michael J.
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081467	A1	20021017	WO 2002-US10596	20020405 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002307114	A1	20021021	AU 2002-307114	20020405 <--
US 20030139398	A1	20030724	US 2002-117542	20020405 <--
US 7081460	B2	20060725		
EP 1389205	A1	20040218	EP 2002-763938	20020405
EP 1389205	B1	20051221		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004529918	T	20040930	JP 2002-579455	20020405
PRIORITY APPLN. INFO.:			US 2001-282648P P	20010409
			WO 2002-US10596 W	20020405

OTHER SOURCE(S): MARPAT 137:294975

AB The invention is directed to novel quinazoline and quinazoline-like derivs. (shown as I (e.g. 6-[(1E)-3-[(4,5-dihydro-1H-imidazol-2-yl)amino]-1-propenyl]-(αS)-3,4-dihydro-4-oxo-α-[[(2,3,4,5,6-pentamethylphenyl)sulfonyl]amino]-2-quinazolinepropanoic acid (shown as II)); and pharmaceutically acceptable racemates, enantiomers, diastereomers and salts thereof), their usefulness as integrin antagonists and methods for the treatment of integrin-mediated disorders. In I, A is carbonyl, amino, carbamoyl, acetamido, acetimido, amidino, iminomethylamino, ureido, biureto, biurea, thioureido, guanidino, biguanido, biguanidino, amidrazone, hydrazo, carbazoyl, semicarbazido, cycloalkylene, heterocyclene, arylene and heteroarylene. (B) is optionally present and is NH, O and C(O); M is C1-C6 alkylene, C2-6 alkenylene, C2-C6 alkynylene and arylene. R3 is 1-2 substituents independently H, C1-C8 alkyl, cycloalkyl, heterocyclo, aryl, aryl(C1-C8)alkyl, heteroaryl, heteroaryl(C1-C8)alkyl, amino, C1-C8 alkylamino, di(C1-C8)alkylamino, imino, iminomethyl, amidino, C1-C8 alkylamidino, di(C1-C8)alkylamidino, cycloalkylamidino, halogen and hydroxy. (L) is optionally present and is NH, O, S and C(O); Y is two substituents joined to the ring by single-bonds and one substituent joined to the ring by a double-bond. X is N, NH, O and S; R1 is optionally present and is H, C1-C8 alkyl, cycloalkyl, cycloalkyl(C1-C6)alkyl, aryl, aryl(C1-C6)alkyl, heteroaryl, heteroaryl(C1-C6)alkyl, arylamino and heteroarylamino; E is C1-C4 alkyl substituted with W and W'; F is C1-C4 alkyl substituted with U and U'. W, W', U and U' are independently H, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, cycloalkyl, cycloalkyl(C1-C4)alkyl, heterocyclo, heterocyclo(C1-C4)alkyl, aryl, aryl(C1-C4)alkyl, biaryl, heteroaryl, heteroaryl(C1-C4)alkyl, -N[(R4),T(R5)] and halogen. R4 is H and C1-C8 alkyl; T is arylene, carbonyl, carboxy, sulfonyl and -C(O)NH-. R5 is H, C1-C8 alkyl, C2-C8

alkenyl, cycloalkyl, heterocyclo, aryl, aryl(C1-C4)alkyl, aryl(C2-C4)alkenyl, biaryl, biaryl(C1-C4)alkyl, heteroaryl, heteroaryl(C1-C4)alkyl and amino. R6 is H, C1-C8 alkyl and (CH2)1-8CON(R7)2; and, R7 is H, C1-C8 alkyl and cycloalkyl. Although the methods of preparation are not claimed, 18 example prepns. are included and 82 specific compds. are claimed. I block vitronectin by binding to isolated αv. beta.3 (demonstrating IC50 values of from .apprx.1 to .apprx.300 nM) and inhibit fibrinogen by binding to isolated GPIIb/IIIa as well. I inhibit integrin-mediated cell-cell or cell-matrix adhesion and, therefore, may be useful in treating integrin mediated disorders including, but not limited to, restenosis, thrombosis, inflammation, atherosclerosis, arthritis, angiogenesis, osteoporosis, bone resorption, tumor cell metastasis, tumor growth, macular degeneration, diabetic retinopathy, and diseases of the lung/airway.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:851117 CAPLUS

DOCUMENT NUMBER: 135:371645

TITLE: Propanoic acid derivatives with acyclic and heterocyclic amidine and guanidine moieties, as αv. beta.3 integrin receptor antagonists, useful for inhibition of neoplasms, bone resorption, etc.

INVENTOR(S): Bandiera, Tiziano; Vianello, Paola; Cozzi, Paolo; Galvani, Arturo

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 155 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087840	A1	20011122	WO 2001-EP4472	20010419 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1282602	A1	20030212	EP 2001-936253	20010419 <--
EP 1282602	B1	20050921		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003533511	T	20031111	JP 2001-584236	20010419 <--
AT 305001	T	20051015	AT 2001-936253	20010419
ES 2248333	T3	20060316	ES 2001-936253	20010419
US 20030144311	A1	20030731	US 2002-258584	20021101 <--
US 6974828	B2	20051213		

PRIORITY APPLN. INFO.: GB 2000-11817 A 20000516
WO 2001-EP4472 W 20010419

OTHER SOURCE(S): MARPAT 135:371645

AB Novel propanoic acid derivs. are integrin receptor antagonists or inhibitors, in particular of the αv.

beta.3 integrin receptor. The compds. are non-peptides of formula I and their pharmaceutically acceptable salts [wherein: G = Q'NHC(:Q)NH- or heterocyclic amidines and guanidines G1-G4; Q = NH or O; Q' = H, C1-6 alk, Ph, phenyl-C1-4-alkyl; X = bond, CH2CONH, (CH2)m, (CH2)mX'; X' = O, S, NH; m = 1-4; B = CONH, CH2CONH, C2-4 alkylene or alkenylene, (CH2)mX'; A = Ph or pyridyl (un)substituted by 1-3 of halo, CF3, C1-4 alkyl, OH, and/or C1-4 alkoxy; Y = O, S, S(O), S(O)2; R = C1-6 alkyl, Ph or C5-7 monoheterocyclyl with 1-3 N/O/S atom(s) and (un)substituted by 1-3 of halo, CF3, C1-4 alkyl, OH, and/or C1-4 alkoxy; R' = H, C1-6 alkyl, C2-4 alkenyl or alkynyl, aryl, aryl-C1-4-alkyl]. The compds. are, for instance, useful for: the treatment of solid tumors by inhibition of angiogenic growth of tumor vessel network, thus promoting tumor regression; inhibition of metastatic spread, thus avoiding cancer metastases; inhibition of bone resorption, thus controlling osteoporosis; inhibition of smooth muscle cells migration into neointima, thus blocking restenosis after percutaneous coronary angioplasty; and the treatment of other pathol. conditions mediated by cell adhesion, cell migration or angiogenesis, such e.g. diabetic retinopathy, rheumatoid arthritis and inflammation. Over 380 specific compds. are claimed. For instance, the pyridine derivative II.2CF3CO2H (PNU 277362F) was prepared by a generalized multi-step synthetic route. When tested in αv. beta.3-vitronectin and .alpha.IIb.beta.3-fibrinogen binding assays, this compound had IC50 values of 0.016 ±0.009 and 9.8 ±4.8 μM, resp., showing highly selective αv. beta. 3-inhibiting activity.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:571738 CAPLUS

DOCUMENT NUMBER: 133:275850

TITLE: Nonpeptide αv. beta.3 Antagonists. 1. Transformation of a Potent, Integrin-Selective .alpha.IIb. beta.3 Antagonist into a Potent αv. beta.3 Antagonist

AUTHOR(S): Duggan, Mark E.; Duong, Le T.; Fisher, John E.; Hamill, Terence G.; Hoffman, William F.; Huff, Joel R.; Ihle, Nathan C.; Leu, Chih-Tai; Nagy, Rose M.; Perkins, James J.; Rodan, Sevgi B.; Wesolowski, Gregg; Whitman, David B.; Zartman, Amy E.; Rodan, Gideon A.; Hartman, George D.

CORPORATE SOURCE: Departments of Medicinal Chemistry Bone Biology and Osteoporosis Research and Pharmacology, Merck Research Laboratories, West Point, PA, 19486, USA

SOURCE: Journal of Medicinal Chemistry (2000), 43(20), 3736-3745
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Modification of the potent fibrinogen receptor (.alpha. IIb.beta.3) antagonist (I) generated compds. with high affinity for the vitronectin receptor αv. beta. 3. Sequential modification of the basic N-terminus of I led to the identification of the 5,6,7,8-tetrahydro[1,8]naphthyridine moiety (THN) as a lipophilic, moderately basic N-terminus that provides mols. with excellent potency and selectivity for the integrin receptor αv. beta.3. The THN-containing analog is a potent inhibitor of bone resorption in vitro and in

vivo. In addition, the identification of a novel, nonpeptide radioligand with high affinity to αv. beta.3 is also reported.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1998:28654 CAPLUS
DOCUMENT NUMBER: 128:106424
ORIGINAL REFERENCE NO.: 128:20771a,20774a
TITLE: Iontophoretic delivery of integrin inhibitors
INVENTOR(S): Hussain, Munir A.; Repta, Arnold J.
PATENT ASSIGNEE(S): Du Pont Merck Pharmaceutical Co., USA
SOURCE: PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9748395	A1	19971224	WO 1997-US10505	19970618 <--
W: AM, AU, AZ, BR, BY, CA, CN, CZ, EE, HU, IL, JP, KG, KR, KZ, LT, LV, MD, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, UA, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9736409	A	19980107	AU 1997-36409	19970618 <--
US 6185453	B1	20010206	US 1997-877829	19970618 <--
PRIORITY APPLN. INFO.:			US 1996-20277P P	19960619
			WO 1997-US10505 W	19970618

OTHER SOURCE(S): MARPAT 128:106424

AB This invention relates to novel methods and devices for iontophoretically administering therapeutic doses of integrin receptor antagonists in a controlled manner through the skin. Such integrin receptor antagonists include but are not limited to antagonists of the IIb/IIIa and g(a)vg(b)3 integrins and related cell surface adhesive protein receptors. The present invention includes iontophoretic delivery devices comprising integrin inhibitors. Such methods and devices are useful, alone or in combination with other therapeutic agents, for the treatment of thromboembolic disorders, angiogenic disorders, inflammation, bone degradation, cancer metastasis, diabetic retinopathy, restenosis, macular degeneration, and other conditions mediated by cell adhesion and/or cell migration and/or angiogenesis. The iontophoretic delivery of a (4-formamidinophenyl)isoxazolinylacetyldiaminopropionic acid derivative through porcine skin was demonstrated.

=> d his

(FILE 'HOME' ENTERED AT 09:11:20 ON 12 SEP 2008)

FILE 'REGISTRY' ENTERED AT 09:11:43 ON 12 SEP 2008
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L4 0 S L1 SSS FULL
L5 STRUCTURE UPLOADED
L6 0 S L2 SSS FULL

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     FILE 'CAPLUS' ENTERED AT 09:16:58 ON 12 SEP 2008
                S L5

     FILE 'REGISTRY' ENTERED AT 09:17:05 ON 12 SEP 2008
L7             0 S L5

     FILE 'CAPLUS' ENTERED AT 09:17:05 ON 12 SEP 2008
L8             0 S L7

     FILE 'REGISTRY' ENTERED AT 09:22:10 ON 12 SEP 2008
L9               SCREEN 1006 AND 2076
L10              STRUCTURE UPLOADED
L11              QUE L10 AND L9
L12            3 S L11 SSS FULL

     FILE 'CAPLUS' ENTERED AT 09:25:09 ON 12 SEP 2008
L13            2 S L12

     FILE 'STNGUIDE' ENTERED AT 09:27:23 ON 12 SEP 2008

     FILE 'CAPLUS' ENTERED AT 09:43:05 ON 12 SEP 2008
L14        36123 S INTEGRINS
L15         5292 S L14 AND INHIBITORS
L16         2727 S L15 AND BETA-3
L17         1901 S L16 AND ALPHA-IIB
L18         1264 S L17 AND PY<=2003
L19            4 S L18 AND SPIRO

     FILE 'STNGUIDE' ENTERED AT 09:44:50 ON 12 SEP 2008
L20            0 S L18 AND "INTEGRIN RECEPTOR"

     FILE 'CAPLUS' ENTERED AT 10:14:04 ON 12 SEP 2008
L21           46 S L18 AND "INTEGRIN RECEPTOR"
L22           46 S L21 AND BETA-3
L23            5 S L22 AND BONE

=> s L22 and "tumor cell"
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        173228 "TUMORS"
        519321 "TUMOR"
                 ("TUMOR" OR "TUMORS")
       2452037 "CELL"
       2113147 "CELLS"
       3204889 "CELL"
                 ("CELL" OR "CELLS")
        104872 "TUMOR CELL"
                 ("TUMOR"(W)"CELL")
L24            2 L22 AND "TUMOR CELL"

=> d L24  1-2 ibib ab

L24  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2004:240410  CAPLUS
DOCUMENT NUMBER:          140:264483
TITLE:                    Cloning and characterization of contortrostatin (CN),
                          a snake venom disintegrin, and methods for its use in
                          preventing metastasis and other conditions
INVENTOR(S):              Markland, Francis S., Jr.; Zhou, Qing
PATENT ASSIGNEE(S):       University of Southern California, USA
SOURCE:                   U.S., 56 pp., Cont.-in-part of U.S. Ser. No. 163,047,
                          abandoned.
```

CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6710030	B1	20040323	US 1999-460295	19991210
US 5731288	A	19980324	US 1996-632691	19960415 <--
US 5814609	A	19980929	US 1996-745603	19961108 <--
CA 2393463	A1	20010614	CA 2000-2393463	20001209 <--
WO 2001041791	A1	20010614	WO 2000-US33367	20001209 <--
WO 2001041791	A9	20020704		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1235586	A1	20020904	EP 2000-984092	20001209 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2000016488	A	20030624	BR 2000-16488	20001209 <--
JP 2004500357	T	20040108	JP 2001-543135	20001209
MX 2002PA05800	A	20031014	MX 2002-PA5800	20020610 <--
US 20040132659	A1	20040708	US 2003-712584	20031112
US 7220724	B2	20070522		
US 20070123458	A1	20070531	US 2006-544190	20061005

PRIORITY APPLN. INFO.:

US 1993-141321	B1	19931022
US 1995-540423	B3	19951010
US 1996-632691	A2	19960415
US 1996-745603	A2	19961108
US 1998-163047	B2	19980929
US 1999-460295	A	19991210
US 2000-591552	A	20000608
WO 2000-US33367	W	20001209
US 2003-439532	A1	20030516
US 2003-712584	A3	20031112

AB The amino acid sequence of native contortrostatin was used in a cloning strategy to obtain full-length cDNA and deduced amino acid sequences for a contortrostatin precursor. The precursor includes pro-protein, metalloproteinase, and disintegrin (contortrostatin) regions of the multidomain protein. The sequences can be used produce recombinant DNA mols. which code on expression for contortrostatin proteins, including biol. active variants and fragments. When formulated as a pharmaceutically acceptable composition, the proteins can be used to treat patients by inhibiting disease processes associated with an integrin binding to an integrin receptor.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:793620 CAPLUS
DOCUMENT NUMBER: 137:294975
TITLE: Preparation of quinazolinepropanoic acids and related compounds for the treatment of integrin-mediated disorders

INVENTOR(S): Hoekstra, William J.; Lawson, Edward C.; Costanzo, Michael J.
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081467	A1	20021017	WO 2002-US10596	20020405 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002307114	A1	20021021	AU 2002-307114	20020405 <--
US 20030139398	A1	20030724	US 2002-117542	20020405 <--
US 7081460	B2	20060725		
EP 1389205	A1	20040218	EP 2002-763938	20020405
EP 1389205	B1	20051221		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004529918	T	20040930	JP 2002-579455	20020405

PRIORITY APPLN. INFO.: US 2001-282648P P 20010409
WO 2002-US10596 W 20020405

OTHER SOURCE(S): MARPAT 137:294975

AB The invention is directed to novel quinazoline and quinazoline-like derivs. (shown as I (e.g. 6-[(1E)-3-[(4,5-dihydro-1H-imidazol-2-yl)amino]-1-propenyl]-(αS)-3,4-dihydro-4-oxo-α-[[(2,3,4,5,6-pentamethylphenyl)sulfonyl]amino]-2-quinazolinepropanoic acid (shown as II)); and pharmaceutically acceptable racemates, enantiomers, diastereomers and salts thereof), their usefulness as integrin antagonists and methods for the treatment of integrin-mediated disorders. In I, A is carbonyl, amino, carbamoyl, acetamido, acetimido, amidino, iminomethylamino, ureido, biureto, biurea, thioureido, guanidino, biguanido, biguanidino, amidrazone, hydrazo, carbazoyl, semicarbazido, cycloalkylene, heterocyclene, arylene and heteroarylene. (B) is optionally present and is NH, O and C(O); M is C1-C6 alkylene, C2-6 alkenylene, C2-C6 alkynylene and arylene. R3 is 1-2 substituents independently H, C1-C8 alkyl, cycloalkyl, heterocyclo, aryl, aryl(C1-C8)alkyl, heteroaryl, heteroaryl(C1-C8)alkyl, amino, C1-C8 alkylamino, di(C1-C8)alkylamino, imino, iminomethyl, amidino, C1-C8 alkylamidino, di(C1-C8)alkylamidino, cycloalkylamidino, halogen and hydroxy. (L) is optionally present and is NH, O, S and C(O); Y is two substituents joined to the ring by single-bonds and one substituent joined to the ring by a double-bond. X is N, NH, O and S; R1 is optionally present and is H, C1-C8 alkyl, cycloalkyl, cycloalkyl(C1-C6)alkyl, aryl, aryl(C1-C6)alkyl, heteroaryl, heteroaryl(C1-C6)alkyl, arylamino and heteroarylamino; E is C1-C4 alkyl substituted with W and W'; F is C1-C4 alkyl substituted with U and U'. W, W', U and U' are independently H, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, cycloalkyl, cycloalkyl(C1-C4)alkyl, heterocyclo, heterocyclo(C1-C4)alkyl, aryl, aryl(C1-C4)alkyl, biaryl, heteroaryl, heteroaryl(C1-C4)alkyl, -N[(R4),T(R5)] and halogen. R4 is H and C1-C8 alkyl; T is arylene,

carbonyl, carboxy, sulfonyl and -C(O)NH-. R5 is H, C1-C8 alkyl, C2-C8 alkenyl, cycloalkyl, heterocyclo, aryl, aryl(C1-C4)alkyl, aryl(C2-C4)alkenyl, biaryl, biaryl(C1-C4)alkyl, heteroaryl, heteroaryl(C1-C4)alkyl and amino. R6 is H, C1-C8 alkyl and (CH2)1-8CON(R7)2; and, R7 is H, C1-C8 alkyl and cycloalkyl. Although the methods of preparation are not claimed, 18 example prepns. are included and 82 specific compds. are claimed. I block vitronectin by binding to isolated αv. beta.3 (demonstrating IC50 values of from .apprx.1 to .apprx.300 nM) and inhibit fibrinogen by binding to isolated GPIIb/IIIa as well. I inhibit integrin-mediated cell-cell or cell-matrix adhesion and, therefore, may be useful in treating integrin mediated disorders including, but not limited to, restenosis, thrombosis, inflammation, atherosclerosis, arthritis, angiogenesis, osteoporosis, bone resorption, tumor cell metastasis, tumor growth, macular degeneration, diabetic retinopathy, and diseases of the lung/airway.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 09:11:20 ON 12 SEP 2008)

FILE 'REGISTRY' ENTERED AT 09:11:43 ON 12 SEP 2008
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L3 0 S L1 SSS FULL
L4 0 S L1 SSS FULL
L5 STRUCTURE UPLOADED
L6 0 S L2 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:16:58 ON 12 SEP 2008
S L5

FILE 'REGISTRY' ENTERED AT 09:17:05 ON 12 SEP 2008
L7 0 S L5

FILE 'CAPLUS' ENTERED AT 09:17:05 ON 12 SEP 2008
L8 0 S L7

FILE 'REGISTRY' ENTERED AT 09:22:10 ON 12 SEP 2008
L9 SCREEN 1006 AND 2076
L10 STRUCTURE UPLOADED
L11 QUE L10 AND L9
L12 3 S L11 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:25:09 ON 12 SEP 2008
L13 2 S L12

FILE 'STNGUIDE' ENTERED AT 09:27:23 ON 12 SEP 2008

FILE 'CAPLUS' ENTERED AT 09:43:05 ON 12 SEP 2008
L14 36123 S INTEGRINS
L15 5292 S L14 AND INHIBITORS
L16 2727 S L15 AND BETA-3
L17 1901 S L16 AND ALPHA-IIB
L18 1264 S L17 AND PY<=2003
L19 4 S L18 AND SPIRO

FILE 'STNGUIDE' ENTERED AT 09:44:50 ON 12 SEP 2008

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L20           0 S L18 AND "INTEGRIN RECEPTOR"

     FILE 'CAPLUS' ENTERED AT 10:14:04 ON 12 SEP 2008
L21          46 S L18 AND "INTEGRIN RECEPTOR"
L22          46 S L21 AND BETA-3
L23           5 S L22 AND BONE
L24           2 S L22 AND "TUMOR CELL"

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         33345 FIBRINOGEN
         19802 FIBRINOGENS
         36894 FIBRINOGEN
                 (FIBRINOGEN OR FIBRINOGENS)
L25        367 L18 AND FIBRINOGEN

=> s L25 and bobe
             1 BOBE
L26          0 L25 AND BOBE

=> s L25 and bone
        234312 BONE
         24682 BONES
        241235 BONE
                 (BONE OR BONES)
L27          6 L25 AND BONE

=> d L27 1-6 ibib ab

L27  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2003:282116  CAPLUS
DOCUMENT NUMBER:          138:304291
TITLE:                    New benzoxazine derivatives useful as αv.
                          beta.3 integrin receptor antagonists
INVENTOR(S):              Vianello, Paola; Bandiera, Tiziano; Varasi, Mario
PATENT ASSIGNEE(S):       Pharmacia & Upjohn, S.P.A., Italy
SOURCE:                   U.S. Pat. Appl. Publ., 37 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     US 20030069236        A1    20030410    US 2001-924732          20010808 <--
     US 6794385            B2    20040921
PRIORITY APPLN. INFO.:                       US 2001-924732          20010808
OTHER SOURCE(S):          MARPAT 138:304291
AB   The invention relates to a class of compds. I, or pharmaceutically
     acceptable salts, prodrugs, or esters thereof [wherein: G = Q'NHCONH-,
     certain cyclic amidines and guanidines, such as pyridin-2-ylamino or
     imidazolin-2-ylamino, optionally substituted by C1-4-alkyl; Q = NH or O;
     Q' = H, C1-6 alkyl, Ph, or phenyl-C1-4-alkyl; B = C1-4 alkyl or C2-4
     alkenyl; A = CH2, O, S(O)0-2, NH, CONH, CON(Me), NHCO, N(Me)CO; R1 = H,
     C1-4 alkyl, C1-4 alkoxy, OH, halo, or CF3; X = bond, CO; R2 = H, C1-4
     alkyl, C3-7 cycloalkyl, C1-4-alkylcycloalkyl; aryl (substituted by 0-3 of:
     halo, CF3, C1-4 alkyl, OH and C1-4 alkoxy), aralkyl, and C5-7 monocyclic
     heteroaryl with 1-3 N/O/S atoms (substituted by 0-3 of: halo, CF3, C1-4
     alkyl, OH, and C1-4 alkoxy); Y = (CH2)1-2; R = H, C1-6 alkyl, C2-4
     alkenyl, C2-4 alkynyl, aryl, or aryl-C1-4 alkyl; provided that X ≠
     bond when G = H2NCONH-].  The invention also relates to pharmaceutical
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compns. comprising I, and to methods of selectively inhibiting or antagonizing αv. beta.3 integrin using I. The compds. can be used for treatment of a variety of medical conditions, including cancer, and can be used or formulated in combination with other classes of antitumor agents. Approx. 50 compds. are specifically claimed, and synthetic details are given for 6 of them. For example, cyclocondensation of 4-nitro-2-aminophenol with Me 4-bromocrotonate using NaHCO3 in MeOH gave 91% Me (6-nitro-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetate. This compound underwent a sequence of: (1) N-phenylation using 1,4-cyclohexanedione and p-MeC6H4SO3H (25%), (2) hydrogenation of nitro to amino (56%), (3) amidation of amino with N-(benzyloxycarbonyl)-N-(1-oxido-2-pyridinyl)-β-alanine (76%), (4) reduction of the N-oxide using SnCl2 and TiCl4 (99%), (5) reductive removal of benzyloxycarbonyl (79.5%), and (6) saponification of the Me ester with aqueous NaOH in EtOH (35%), to give title compound II [m = 1].. Three standard formulations of the similarly prepared II [m = 2] are described. I [m = 2] bound to human αv. beta. 3 receptor in vitro with an IC50 of 0.024 μM, and to human . alpha.IIb.beta.3 receptor with an IC50 of 27 μM, thus giving a high selectivity ratio of approx. 1000 for αv. beta.3.

L27 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:907166 CAPLUS
DOCUMENT NUMBER: 138:322
TITLE: Plasma glucosylceramide deficiency as risk factor for thrombosis and modulator of anticoagulant protein C
INVENTOR(S): Griffin, John H.; Deguchi, Hiroshi; Fernandez, Jose
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 32 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020177563	A1	20021128	US 2002-86943	20020228 <--
US 6756208	B2	20040629		
WO 2002102325	A2	20021227	WO 2002-US6340	20020228 <--
WO 2002102325	A3	20030912		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002326291	A1	20030102	AU 2002-326291	20020228 <--
EP 1370570	A2	20031217	EP 2002-760992	20020228 <--
EP 1370570	B1	20070124		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
AT 352309	T	20070215	AT 2002-760992	20020228
US 20040132688	A1	20040708	US 2003-739962	20031217
PRIORITY APPLN. INFO.:			US 2001-272103P P	20010228

	US 2001-278045P	P	20010322
	US 2002-86943	A3	20020228
	WO 2002-US6340	W	20020228

AB The present invention has determined that exogenously added glucosylceramide (GlcCer) and other neutral glycolipids such as the homologous Glc-containing globotriaosylceramide (Gb3Cer), dose-dependently prolonged clotting times of normal plasma in the presence but not absence of APC:protein S, indicating GlcCer or Gb3Cer can enhance protein C pathway anticoagulant activity. In studies using purified proteins, inactivation of factor Va by APC:protein S was enhanced by GlcCer alone and by GlcCer, globotriaosylceramide, lactosylceramide, and galactosylceramide in multicomponent vesicles containing phosphatidylserine and phosphatidylcholine. Thus, the present invention provides neutral glycolipids such as GlcCer and Gb3Cer, as anticoagulant cofactors that contribute to the antithrombotic activity of the protein C pathway. The present invention has also determined that a deficiency of plasma GlcCer is a risk factor for thrombosis. Methods are provided to determine individuals at risk for thrombosis, methods of treatment as well as methods of screening for antithrombotic factors from neutral glycolipids.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:793620 CAPLUS

DOCUMENT NUMBER: 137:294975

TITLE: Preparation of quinazolinepropanoic acids and related compounds for the treatment of integrin-mediated disorders

INVENTOR(S): Hoekstra, William J.; Lawson, Edward C.; Costanzo, Michael J.

PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA

SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081467	A1	20021017	WO 2002-US10596	20020405 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002307114	A1	20021021	AU 2002-307114	20020405 <--
US 20030139398	A1	20030724	US 2002-117542	20020405 <--
US 7081460	B2	20060725		
EP 1389205	A1	20040218	EP 2002-763938	20020405
EP 1389205	B1	20051221		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004529918	T	20040930	JP 2002-579455	20020405

PRIORITY APPLN. INFO.:	US 2001-282648P	P	20010409
	WO 2002-US10596	W	20020405

OTHER SOURCE(S): MARPAT 137:294975

AB The invention is directed to novel quinazoline and quinazoline-like derivs. (shown as I (e.g. 6-[(1E)-3-[(4,5-dihydro-1H-imidazol-2-yl)amino]-1-propenyl]-(αS)-3,4-dihydro-4-oxo-α-[[(2,3,4,5,6-pentamethylphenyl)sulfonyl]amino]-2-quinazolinepropanoic acid (shown as II)); and pharmaceutically acceptable racemates, enantiomers, diastereomers and salts thereof), their usefulness as integrin antagonists and methods for the treatment of integrin-mediated disorders. In I, A is carbonyl, amino, carbamoyl, acetamido, acetimido, amidino, iminomethylamino, ureido, biureto, biurea, thioureido, guanidino, biguanido, biguanidino, amidrazone, hydrazo, carbazoyl, semicarbazido, cycloalkylene, heterocyclene, arylene and heteroarylene. (B) is optionally present and is NH, O and C(O); M is C1-C6 alkylene, C2-6 alkenylene, C2-C6 alkynylene and arylene. R3 is 1-2 substituents independently H, C1-C8 alkyl, cycloalkyl, heterocyclo, aryl, aryl(C1-C8)alkyl, heteroaryl, heteroaryl(C1-C8)alkyl, amino, C1-C8 alkylamino, di(C1-C8)alkylamino, imino, iminomethyl, amidino, C1-C8 alkylamidino, di(C1-C8)alkylamidino, cycloalkylamidino, halogen and hydroxy. (L) is optionally present and is NH, O, S and C(O); Y is two substituents joined to the ring by single-bonds and one substituent joined to the ring by a double-bond. X is N, NH, O and S; R1 is optionally present and is H, C1-C8 alkyl, cycloalkyl, cycloalkyl(C1-C6)alkyl, aryl, aryl(C1-C6)alkyl, heteroaryl, heteroaryl(C1-C6)alkyl, arylamino and heteroarylamino; E is C1-C4 alkyl substituted with W and W'; F is C1-C4 alkyl substituted with U and U'. W, W', U and U' are independently H, C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, cycloalkyl, cycloalkyl(C1-C4)alkyl, heterocyclo, heterocyclo(C1-C4)alkyl, aryl, aryl(C1-C4)alkyl, biaryl, heteroaryl, heteroaryl(C1-C4)alkyl, -N[(R4),T(R5)] and halogen. R4 is H and C1-C8 alkyl; T is arylene, carbonyl, carboxy, sulfonyl and -C(O)NH-. R5 is H, C1-C8 alkyl, C2-C8 alkenyl, cycloalkyl, heterocyclo, aryl, aryl(C1-C4)alkyl, aryl(C2-C4)alkenyl, biaryl, biaryl(C1-C4)alkyl, heteroaryl, heteroaryl(C1-C4)alkyl and amino. R6 is H, C1-C8 alkyl and (CH2)1-8CON(R7)2; and, R7 is H, C1-C8 alkyl and cycloalkyl. Although the methods of preparation are not claimed, 18 example prepns. are included and 82 specific compds. are claimed. I block vitronectin by binding to isolated αv. beta.3 (demonstrating IC50 values of from .apprx.1 to .apprx.300 nM) and inhibit fibrinogen by binding to isolated GPIIb/IIIa as well. I inhibit integrin-mediated cell-cell or cell-matrix adhesion and, therefore, may be useful in treating integrin mediated disorders including, but not limited to, restenosis, thrombosis, inflammation, atherosclerosis, arthritis, angiogenesis, osteoporosis, bone resorption, tumor cell metastasis, tumor growth, macular degeneration, diabetic retinopathy, and diseases of the lung/airway.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:851117 CAPLUS

DOCUMENT NUMBER: 135:371645

TITLE: Propanoic acid derivatives with acyclic and heterocyclic amidine and guanidine moieties, as αv. beta.3 integrin receptor antagonists, useful for inhibition of neoplasms, bone resorption, etc.

INVENTOR(S): Bandiera, Tiziano; Vianello, Paola; Cozzi, Paolo; Galvani, Arturo

PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy

SOURCE: PCT Int. Appl., 155 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087840	A1	20011122	WO 2001-EP4472	20010419 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1282602	A1	20030212	EP 2001-936253	20010419 <--
EP 1282602	B1	20050921		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003533511	T	20031111	JP 2001-584236	20010419 <--
AT 305001	T	20051015	AT 2001-936253	20010419
ES 2248333	T3	20060316	ES 2001-936253	20010419
US 20030144311	A1	20030731	US 2002-258584	20021101 <--
US 6974828	B2	20051213		

PRIORITY APPLN. INFO.: GB 2000-11817 A 20000516
WO 2001-EP4472 W 20010419

OTHER SOURCE(S): MARPAT 135:371645

AB Novel propanoic acid derivs. are integrin receptor antagonists or inhibitors, in particular of the αv. beta.3 integrin receptor. The compds. are non-peptides of formula I and their pharmaceutically acceptable salts [wherein: G = Q'NHC(:Q)NH- or heterocyclic amidines and guanidines G1-G4; Q = NH or O; Q' = H, C1-6 alk, Ph, phenyl-C1-4-alkyl; X = bond, CH2CONH, (CH2)m, (CH2)mX'; X' = O, S, NH; m = 1-4; B = CONH, CH2CONH, C2-4 alkylene or alkenylene, (CH2)mX'; A = Ph or pyridyl (un)substituted by 1-3 of halo, CF3, C1-4 alkyl, OH, and/or C1-4 alkoxy; Y = O, S, S(O), S(O)2; R = C1-6 alkyl, Ph or C5-7 monoheterocyclyl with 1-3 N/O/S atom(s) and (un)substituted by 1-3 of halo, CF3, C1-4 alkyl, OH, and/or C1-4 alkoxy; R' = H, C1-6 alkyl, C2-4 alkenyl or alkynyl, aryl, aryl-C1-4-alkyl]. The compds. are, for instance, useful for: the treatment of solid tumors by inhibition of angiogenic growth of tumor vessel network, thus promoting tumor regression; inhibition of metastatic spread, thus avoiding cancer metastases; inhibition of bone resorption, thus controlling osteoporosis; inhibition of smooth muscle cells migration into neointima, thus blocking restenosis after percutaneous coronary angioplasty; and the treatment of other pathol. conditions mediated by cell adhesion, cell migration or angiogenesis, such e.g. diabetic retinopathy, rheumatoid arthritis and inflammation. Over 380 specific compds. are claimed. For instance, the pyridine derivative II.2CF3CO2H (PNU 277362F) was prepared by a generalized multi-step synthetic route. When tested in αv. beta.3-vitronectin and .alpha.IIb. beta.3-fibrinogen binding assays, this compound had IC50 values of 0.016 ±0.009 and 9.8 ±4.8 μM, resp., showing highly selective αv. beta.3-inhibiting activity.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:24445 CAPLUS
DOCUMENT NUMBER: 135:116824
TITLE: Safety and preliminary efficacy of one month

glycoprotein IIb/IIIa inhibition with lefradafiban in patients with acute coronary syndromes without ST-elevation: A phase II study

AUTHOR(S): Akkerhuis, K. M.; Neuhaus, K.-L.; Wilcox, R. G.; Vahanian, A.; Boland, J.-L.; Hoffmann, J.; Baardman, T.; Nehmiz, G.; Roth, U.; Klootwijk, A. P. J.; Deckers, J. W.; Simoons, M. L.

CORPORATE SOURCE: Thoraxcenter, Erasmus University and University Hospital Rotterdam, Rotterdam, 3000 CC, Neth.

SOURCE: European Heart Journal (2000), 21(24), 2042-2055
CODEN: EHJODF; ISSN: 0195-668X
PUBLISHER: W. B. Saunders Co. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oral glycoprotein IIb/IIIa inhibitors might enhance the early benefit of an i.v. agent and prevent subsequent cardiac events in patients with acute coronary syndromes. We assessed the safety and preliminary efficacy of 1 mo treatment with three dose levels of the oral GP IIb/IIIa blocker lefradafiban in patients with unstable angina or myocardial infarction without persistent ST elevation. The Fibrinogen Receptor Occupancy STudy (FROST) was designed as a dose-escalation trial with 20, 30 and 45 mg lefradafiban t.i.d. or placebo. Five hundred and thirty-one patients were randomized in a 3:1 ratio to lefradafiban or placebo in a double-blind manner. Efficacy was assessed by the incidence of death, myocardial infarction, coronary revascularization and recurrent angina. Safety was evaluated by the occurrence of bleeding classified according to the TIMI criteria and by measuring clin. laboratory parameters. There was a trend towards a reduction in cardiac events with lefradafiban 30 mg when compared with placebo and lefradafiban 20 mg. The benefit was particularly apparent in patients with a pos. (≥0.1 ng•ml-1) troponin I test at baseline and less so in those with a neg. test result. In patients receiving lefradafiban, the cardiac event rate decreased with increasing minimal levels of fibrinogen receptor occupancy. There was a dose-dependent increase in the incidence of bleeding: the composite of major or minor bleeding occurred in 1% of placebo patients, 5% of patients receiving lefradafiban 20 mg and in 7% of patients receiving 30 mg, with an excessive risk (15%) in the 45 mg group which resulted in early discontinuation of this dose level. Gingival and arterial or venous puncture site bleedings were most common and accounted for more than 60% of all hemorrhagic events. There was an increased incidence of neutropenia (neutrophils <1.5 + 109/l) in the lefradafiban groups (5.2% vs 1.5% in the placebo group), which did not result from bone marrow depression but rather from a reversible redistribution of neutrophils by margination or clustering. One month's treatment with the oral glycoprotein IIb/IIIa inhibitor lefradafiban in patients with unstable angina and myocardial infarction without persistent ST elevation resulted in a decrease in cardiac events with lefradafiban 30 mg and a dose-dependent increase in hemorrhagic events. The observed favorable trend towards a reduction in cardiac events in patients with elevated troponin levels requires confirmation in a large clin. trial.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:571738 CAPLUS
DOCUMENT NUMBER: 133:275850

TITLE: Nonpeptide αv. beta.3 Antagonists. 1. Transformation of a Potent, Integrin-Selective .alpha.IIb. beta.3 Antagonist into a Potent

αv. beta.3 Antagonist
AUTHOR(S): Duggan, Mark E.; Duong, Le T.; Fisher, John E.; Hamill, Terence G.; Hoffman, William F.; Huff, Joel R.; Ihle, Nathan C.; Leu, Chih-Tai; Nagy, Rose M.; Perkins, James J.; Rodan, Sevgi B.; Wesolowski, Gregg; Whitman, David B.; Zartman, Amy E.; Rodan, Gideon A.; Hartman, George D.
CORPORATE SOURCE: Departments of Medicinal Chemistry Bone Biology and Osteoporosis Research and Pharmacology, Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Journal of Medicinal Chemistry (2000), 43(20), 3736-3745
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Modification of the potent fibrinogen receptor (.alpha .IIb.beta.3) antagonist (I) generated compds. with high affinity for the vitronectin receptor αv. beta.3. Sequential modification of the basic N-terminus of I led to the identification of the 5,6,7,8-tetrahydro[1,8]naphthyridine moiety (THN) as a lipophilic, moderately basic N-terminus that provides mols. with excellent potency and selectivity for the integrin receptor αv. beta.3. The THN-containing analog is a potent inhibitor of bone resorption in vitro and in vivo. In addition, the identification of a novel, nonpeptide radioligand with high affinity to αv. beta.3 is also reported.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s L25 and spiro
26150 SPIRO
20 SPIROS
26167 SPIRO
(SPIRO OR SPIROS)
L28 2 L25 AND SPIRO

=> d L28 1-2 ibib ab

L28 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:923795 CAPLUS
DOCUMENT NUMBER: 136:53749
TITLE: Preparation of heteroarylalkanoic acids as integrin receptor antagonists
INVENTOR(S): Nagarajan, Scrinivasan Raj; Khanna, Ish Kumar; Tollefson, Michael B.; Mohler, Scott B.; Chen, Barbara; Russell, Mark; Devadas, Balekudru; Penning, Thomas D.; Schretzman, Lori A.; Spangler, Dale P.; Boys, Mark Laurence; Chandrakumar, Nizal Samuel; Lu, Hwang-Fun
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 368 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001096334 A2 20011220 WO 2001-US19375 20010615 <--
WO 2001096334 A3 20020912
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 20020133023 A1 20020919 US 2001-881913 20010615 <--
US 6933304 B2 20050823
EP 1289983 A2 20030312 EP 2001-948424 20010615 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004511434 T 20040415 JP 2002-510476 20010615
US 20040092497 A1 20040513 US 2003-311385 20030905
US 7119098 B2 20061010
PRIORITY APPLN. INFO.: US 2000-211781P P 20000615
US 2000-211782P P 20000615
WO 2001-US19375 W 20010615

OTHER SOURCE(S): MARPAT 136:53749

AB Title compds. A1Z2Z1AXYY5(Y3)(Y4)CH2CORb [I; wherein ring A = (un)substituted 4-8 membered monocyclic or 7-12 membered bicyclic ring containing 1-4 heteroatoms, selected from O, N, or S; A1 = (un)substituted 5-9 membered monocyclic or 7-14 membered polycyclic heterocycle containing at least 1 N and optionally 1-4 heteroatoms or groups selected from O, N, S, SO2, or CO; Z1 = CH2, O, CH2O, NH, CO, S, SO, CH(OH), and SO2; Z2 = (un)substituted 1-5 C linker optionally containing 1 or more heteroatoms selected from O, S, and N; Z1Z2 may contain a carboxamide, sulfone, sulfonamide, alkenyl, alkynyl, acyl, or (un)substituted 5- or 6-membered (hetero)aryl; X = CHRe, NRf, O, S, SO2, or CO; Re = H, (cyclo)alkyl, alkoxy(alkyl), OH, alkynyl, alkenyl, haloalkyl, thioalkyl, or aryl; Rf = H, (halo)alkyl, aryl, or benzyl; Y = (CH2)p, CHRg, NRg, CO, or SO2; Rg = H, (halo)alkyl, alkoxyalkyl, alkynyl, (hetero)aryl, OH, alkoxy, or carboxyalkyl; p = 0-1; XY may contain acyl, alkyl, sulfonyl, amino, (thio)ether, carboxamido, sulfonamido, aminosulfonyl, or olefin; Y3 and Y4 = independently H, (halo)alkyl, halo, (hetero)aryl, hydroxyalkyl, alkynyl, etc.; Rb = X2Rh; X2 = O, S, or NRj; Rh and Rj = independently H, (ar)alkyl, acyl, or alkoxyalkyl; with provisos] and their pharmaceutically acceptable salts were prepared for selectively antagonizing the αv. beta.3 and/or the αvβ5 integrin without significantly antagonizing the fibrinogen IIb/IIIa integrin. For example, 3-(hydroxymethyl)benzonitrile was protected with 3,4-dihydro-2H-pyran (89%) and treated with HONH2•HCl to give the benzenecarboximidamide (98%). Cyclization with 3-methylglutaric anhydride in the presence of MeI (64%) and deprotection (98%) gave the Me 1,2,4-oxadiazolebutanoate (64%). Oxidation to the aldehyde, followed by reductive addition of 2-aminopyridine and workup, afforded the oxadiazolebutanoic acid (II). In vitronectin adhesion assays, I antagonized the αv. beta.3 integrin and the αvβ5 integrin with IC50 values of 0.1 nM to 100 μM and < 50 μM, resp. I are useful for the treatment of tumor metastasis, solid tumor growth, angiogenesis, osteoporosis, humoral hypercalcemia of malignancy, smooth muscle cell migration, restenosis, atherosclerosis, macular degeneration, retinopathy, and arthritis (no data).

L28 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:398915 CAPLUS
DOCUMENT NUMBER: 125:137093

ORIGINAL REFERENCE NO.: 125:25553a,25556a
TITLE: Non-Peptide glycoprotein IIb/IIIa inhibitors . 9. Centrally constrained alpha-sulfonamides are useful tools for exploring platelet receptor function
AUTHOR(S): Egbertson, M. S.; Bednar, B.; Bednar, R. A.; Hartman, G. D.; Gould, R. J.; Lynch, R. J.; Vassallo, L. M.; Young, S. D.
CORPORATE SOURCE: Dept. Medicinal Chem., Merck Res. Laboratories, West Point, PA, 19486, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(12), 1415-1420
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two fluorescent, centrally constrained fibrinogen receptor antagonists were prepared to probe ligand receptor interactions. The use of these centrally constrained fibrinogen receptor antagonists to characterize the binding affinity of nonfluorescent antagonists to inactive isolated GPIIb/IIIa and GPIIb/IIIa on platelets is described.

=> d his

(FILE 'HOME' ENTERED AT 09:11:20 ON 12 SEP 2008)

FILE 'REGISTRY' ENTERED AT 09:11:43 ON 12 SEP 2008
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 0 S L1 SSS FULL
L4 0 S L1 SSS FULL
L5 STRUCTURE UPLOADED
L6 0 S L2 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:16:58 ON 12 SEP 2008
S L5

FILE 'REGISTRY' ENTERED AT 09:17:05 ON 12 SEP 2008
L7 0 S L5

FILE 'CAPLUS' ENTERED AT 09:17:05 ON 12 SEP 2008
L8 0 S L7

FILE 'REGISTRY' ENTERED AT 09:22:10 ON 12 SEP 2008
L9 SCREEN 1006 AND 2076
L10 STRUCTURE UPLOADED
L11 QUE L10 AND L9
L12 3 S L11 SSS FULL

FILE 'CAPLUS' ENTERED AT 09:25:09 ON 12 SEP 2008
L13 2 S L12

FILE 'STNGUIDE' ENTERED AT 09:27:23 ON 12 SEP 2008

FILE 'CAPLUS' ENTERED AT 09:43:05 ON 12 SEP 2008
L14 36123 S INTEGRINS
L15 5292 S L14 AND INHIBITORS
L16 2727 S L15 AND BETA-3
L17 1901 S L16 AND ALPHA-IIB
L18 1264 S L17 AND PY<=2003
L19 4 S L18 AND SPIRO

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     FILE 'STNGUIDE' ENTERED AT 09:44:50 ON 12 SEP 2008
L20           0 S L18 AND "INTEGRIN RECEPTOR"

     FILE 'CAPLUS' ENTERED AT 10:14:04 ON 12 SEP 2008
L21          46 S L18 AND "INTEGRIN RECEPTOR"
L22          46 S L21 AND BETA-3
L23           5 S L22 AND BONE
L24           2 S L22 AND "TUMOR CELL"
L25         367 S L18 AND FIBRINOGEN
L26           0 S L25 AND BOBE
L27           6 S L25 AND BONE
L28           2 S L25 AND SPIRO

=> s fibrinogen
         33345 FIBRINOGEN
         19802 FIBRINOGENS
L29      36894 FIBRINOGEN
                (FIBRINOGEN OR FIBRINOGENS)

=> s l29 and receptors
        708570 RECEPTORS
L30       2769 L29 AND RECEPTORS

=> s l30 and inhibitors
        583578 INHIBITORS
L31        635 L30 AND INHIBITORS

=> s L31 and (tumor or cancer)
        466089 TUMOR
        173228 TUMORS
        519321 TUMOR
                (TUMOR OR TUMORS)
        374012 CANCER
         54992 CANCERS
        387795 CANCER
                (CANCER OR CANCERS)
L32        174 L31 AND (TUMOR OR CANCER)

=> s L32 and (bone or skeletal)
        234312 BONE
         24682 BONES
        241235 BONE
                (BONE OR BONES)
         97952 SKELETAL
             3 SKELETALS
         97955 SKELETAL
                (SKELETAL OR SKELETALS)
L33         64 L32 AND (BONE OR SKELETAL)

=> S L33 and PY<=2003
      24009633 PY<=2003
L34         16 L33 AND PY<=2003

=> d L34 1-16 ibib ab

L34  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        2003:282116  CAPLUS
DOCUMENT NUMBER:         138:304291
TITLE:                   New benzoxazine derivatives useful as αvβ3
                         integrin receptor antagonists
```

INVENTOR(S): Vianello, Paola; Bandiera, Tiziano; Varasi, Mario
PATENT ASSIGNEE(S): Pharmacia & Upjohn, S.P.A., Italy
SOURCE: U.S. Pat. Appl. Publ., 37 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20030069236	A1	20030410	US 2001-924732	20010808 <--
US 6794385	B2	20040921		
PRIORITY APPLN. INFO.:			US 2001-924732	20010808

OTHER SOURCE(S): MARPAT 138:304291

AB The invention relates to a class of compds. I, or pharmaceutically acceptable salts, prodrugs, or esters thereof [wherein: G = Q'NHCONH-, certain cyclic amidines and guanidines, such as pyridin-2-ylamino or imidazolin-2-ylamino, optionally substituted by C1-4-alkyl; Q = NH or O; Q' = H, C1-6 alkyl, Ph, or phenyl-C1-4-alkyl; B = C1-4 alkyl or C2-4 alkenyl; A = CH2, O, S(O)0-2, NH, CONH, CON(Me), NHCO, N(Me)CO; R1 = H, C1-4 alkyl, C1-4 alkoxy, OH, halo, or CF3; X = bond, CO; R2 = H, C1-4 alkyl, C3-7 cycloalkyl, C1-4-alkylcycloalkyl; aryl (substituted by 0-3 of: halo, CF3, C1-4 alkyl, OH and C1-4 alkoxy), aralkyl, and C5-7 monocyclic heteroaryl with 1-3 N/O/S atoms (substituted by 0-3 of: halo, CF3, C1-4 alkyl, OH, and C1-4 alkoxy); Y = (CH2)1-2; R = H, C1-6 alkyl, C2-4 alkenyl, C2-4 alkynyl, aryl, or aryl-C1-4 alkyl; provided that X ≠ bond when G = H2NCONH-]. The invention also relates to pharmaceutical compns. comprising I, and to methods of selectively inhibiting or antagonizing αvβ3 integrin using I. The compds. can be used for treatment of a variety of medical conditions, including cancer , and can be used or formulated in combination with other classes of antitumor agents. Approx. 50 compds. are specifically claimed, and synthetic details are given for 6 of them. For example, cyclocondensation of 4-nitro-2-aminophenol with Me 4-bromocrotonate using NaHCO3 in MeOH gave 91% Me (6-nitro-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetate. This compound underwent a sequence of: (1) N-phenylation using 1,4-cyclohexanedione and p-MeC6H4SO3H (25%), (2) hydrogenation of nitro to amino (56%), (3) amidation of amino with N-(benzyloxycarbonyl)-N-(1-oxido-2-pyridinyl)-β-alanine (76%), (4) reduction of the N-oxide using SnCl2 and TiCl4 (99%), (5) reductive removal of benzyloxycarbonyl (79.5%), and (6) saponification of the Me ester with aqueous NaOH in EtOH (35%), to give title compound II [m = 1].. Three standard formulations of the similarly prepared II [m = 2] are described. I [m = 2] bound to human αvβ3 receptor in vitro with an IC50 of 0.024 μM, and to human αIIbβ3 receptor with an IC50 of 27 μM, thus giving a high selectivity ratio of approx. 1000 for αvβ3.

L34 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:937303 CAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
JP 2002355079	A	20021210	JP 2002-69354		20020313 <--
PRIORITY APPLN. INFO.:			JP 2001-73183	A	20010314
			JP 2001-74993	A	20010315
			JP 2001-102519	A	20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L34 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:832815 CAPLUS
DOCUMENT NUMBER: 137:348175
TITLE: Use of non-native tRNAs and amino acyl tRNA synthetases with relaxed substrate specificity in the in vivo incorporation of unnatural amino acids
INVENTOR(S): Schultz, Peter; Wang, Lei; Anderson, John Christopher; Chin, Jason W. K.; Liu, David R.; Magliery, Thomas J.; Meggers, Eric L.; Mehl, Ryan Aaron; Pastrnak, Miro; Santoro, Steven William; Zhang, Zhiwen
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 188 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002085923	A2	20021031	WO 2002-US12465	20020419 <--
WO 2002085923	A3	20040527		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2443757	A1	20021031	CA 2002-2443757	20020419 <--
AU 2002256292	A1	20021105	AU 2002-256292	20020419 <--
AU 2002256292	B2	20071206		
US 20030082575	A1	20030501	US 2002-126927	20020419 <--

US 7045337	B2	20060516			
US 20030108885	A1	20030612	US 2002-126931		20020419 <--
US 7083970	B2	20060801			
EP 1490483	A2	20041229	EP 2002-725743		20020419
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
JP 2005502322	T	20050127	JP 2002-583449		20020419
MX 2003PA09563	A	20041206	MX 2003-PA9563		20031017
US 20060063244	A1	20060323	US 2004-2387		20041201
US 20050208536	A1	20050922	US 2004-9635		20041210
US 20050250183	A1	20051110	US 2004-17550		20041217
US 20060233744	A1	20061019	US 2005-254161		20051018
US 7368275	B2	20080506			
US 20060234367	A1	20061019	US 2005-254170		20051018
US 7354761	B2	20080408			
US 20070117184	A1	20070524	US 2006-583551		20061018
US 20080166783	A1	20080710	US 2007-800455		20070504
US 20080167243	A1	20080710	US 2007-978188		20071026
AU 2007251897	A1	20080124	AU 2007-251897		20071220
AU 2008200780	A1	20080313	AU 2008-200780		20080219
PRIORITY APPLN. INFO.:			US 2001-285030P	P	20010419
			US 2002-355514P	P	20020206
			AU 2002-256292	A3	20020419
			AU 2002-303431	A3	20020419
			US 2002-126927	A1	20020419
			US 2002-126931	A3	20020419
			WO 2002-US12465	W	20020419
			US 2004-17550	A1	20041217
			US 2006-583551	A1	20061018

OTHER SOURCE(S): MARPAT 137:348175

AB The invention provides methods and compns. for in vivo incorporation of unnatural amino acids. Also provided are compns. including proteins with unnatural amino acids. Incorporation is achieved by using a non-native or orthogonal tRNA and its cognate aminoacyl tRNA synthetase. The synthetase is modified to accept a range of amino acid analogs as substrates for the charging of the tRNA. The tRNA can also be modified to create a four- or five base anticodon that can be used to limit the incorporation of the foreign amino acid to specific sites, i.e. as a suppressor tRNA. Use of the CUA tRNA and tyrosyl tRNA synthetase of Methanococcus jannaschii to incorporate tyrosine analogs into proteins in Escherichia coli is demonstrated. L-3-(2-Naphthyl)alanine was incorporated into chloramphenicol acetyltransferase at non-essential sites using an amber suppressor tRNA. Resistance of these variants to chloramphenicol was improved by incorporation of L-3-(2-naphthyl)alanine into the culture medium.

L34 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:849246 CAPLUS
DOCUMENT NUMBER: 136:338052
TITLE: Gene profiling of human fetal and adult adrenals
AUTHOR(S): Rainey, W. E.; Carr, B. R.; Wang, Z-N.; Parker, C. R., Jr.
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, Southwestern Medical Center, University of Texas, Dallas, TX, 75390, USA
SOURCE: Journal of Endocrinology (2001), 171(2), 209-215
CODEN: JOENAK; ISSN: 0022-0795
PUBLISHER: Society for Endocrinology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanisms that lead to the steroidogenic differences in the human fetal adrenal (HFA) and adult adrenal gland are not known. However, gene expression clearly plays a critical role in defining their distinct steroidogenic and structural phenotypes. We used DNA microarrays to compare expression levels of several thousand transcripts between the HFA and adult adrenal gland. Total RNA was isolated from 18 HFA and 12 adult adrenal glands. Samples of total RNA were used to make five pools of poly A+ RNA (mRNA). Gene profiling was done using five independent microarrays that contained between 7075 and 9182 cDNA elements. Sixty-nine transcripts were found to have a greater than 2.5-fold difference in expression between HFA and adult adrenals. The largest differences were observed for transcripts that encode IGF-II (25-fold higher in HFA) and 3β-hydroxysteroid dehydrogenase (24-fold higher in adult). Among the other genes, transcripts related to sterol biosynthesis or to growth and development were higher in the HFA than adult adrenals. Transcripts concerned with cellular immunity and signal transduction were preferentially expressed in the adult adrenal. The vast majority of the 69 transcripts have not been studied with regard to adrenal function. Thus, these gene profiles provide valuable information that could help define the mechanisms that control adrenal function.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:828415 CAPLUS

DOCUMENT NUMBER: 137:89412

TITLE: Detection of variations in the DNA methylation profile of genes in the determining the risk of disease

INVENTOR(S): Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander

PATENT ASSIGNEE(S): Epigenomics A.-G., Germany

SOURCE: PCT Int. Appl., 636 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 69

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077373	A2	20011018	WO 2001-XA1486	20010406 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG				
DE 10019058	A1	20011220	DE 2000-10019058	20000406 <--
WO 2001077373	A2	20011018	WO 2001-DE1486	20010406 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001077487	A	20011023	AU 2001-77487	20010406 <--
EP 1360319	A2	20031112	EP 2001-955278	20010406 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

AT 339520	T	20061015	AT 2002-90203		20020605
ES 2272636	T3	20070501	ES 2002-90203		20020605
US 20040067491	A1	20040408	US 2003-240454		20030311
AU 2003204553	A1	20040108	AU 2003-204553		20030605
AU 2003204553	B2	20071129			
JP 2004008217	A	20040115	JP 2003-160375		20030605
US 20040023279	A1	20040205	US 2003-455212		20030605
AU 2006203475	A1	20060831	AU 2006-203475		20060811
AU 2006213968	A1	20061019	AU 2006-213968		20060915
AU 2006225250	A1	20061026	AU 2006-225250		20061005
PRIORITY APPLN. INFO.:			DE 2000-10019058	A	20000406
			WO 2001-DE1486	W	20010406
			DE 2000-10019173	A	20000407
			DE 2000-10032529	A	20000630
			DE 2000-10043826	A	20000901
			AU 2001-275663	A	20010406
			AU 2001-276331	A3	20010406
			AU 2001-75663	A	20010406
			WO 2001-EP4016	W	20010406
			EP 2002-90203	A	20020605
			AU 2006-230475	A	20060811

AB The invention relates to an oligonucleotide kit as probe for the detection of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for determining the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for determining the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or associated syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction. This abstract record is one of several records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.

L34 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2001:338762 CAPLUS
DOCUMENT NUMBER:	134:362292
TITLE:	Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S):	Farr, Spencer
PATENT ASSIGNEE(S):	Phase-1 Molecular Toxicology, USA
SOURCE:	PCT Int. Appl., 222 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001032928 A2 20010510 WO 2000-US30474 20001103 <--
WO 2001032928 A3 20020725
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of individuals to a given agent, such as drug or other chemical, in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

L34 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:50632 CAPLUS
DOCUMENT NUMBER: 134:100897
TITLE: Benzazepinone and quinazoline derivatives inhibiting the binding of adhesive proteins to vitronectin receptors.
INVENTOR(S): Alig, Leo; Chucholowski, Alexander; Weller, Thomas
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE
WO 2001004103 A1 20010118 WO 2000-EP6418 20000706 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 6506744 B1 20030114 US 2000-611700 20000707 <--

PRIORITY APPLN. INFO.: EP 1999-113708 A 19990713
OTHER SOURCE(S): MARPAT 134:100897

AB Compds. of formula (I) wherein R1 is CH2(C:O)NHCHR5CH2COOH or (CH2)m[CH(C6H4R6)]nCH2COOH; R2 is NH(C:O)NHR4 or N:C(NHR10)NHR11; R3 is H, alkyl, cycloalkyl, aralkyl, aryl, carboxyalkyl; R4 is alkyl or aralkyl; R5 is H, alkyl, aryl, heterocyclyl, or (C:O)NHR8; R6 is H or NH(C:O)NHR4; R7 is H, alkyl, cycloalkyl or aralkyl; R8 is alkyl, cycloalkyl, aralkyl or aryl; R9 is H, alkyl, cycloalkyl, aryl or aralkyl; R10 and R11 are each independently H or alkyl or R10 and R11 together with the N-atoms to which they are attached form a 5- to 6-membered heterocyclic ring which can be alkyl-substituted; X is CHR3; Z is NR7 or oxygen, wherein Y is CO when Z is NR7 and Y is CHR9 when Z is oxygen; m, n, and p are zero or whole pos. nos., wherein m is 2 to 5, n is zero or 1, p is zero or 1, as well as pharmaceutically usable salts and esters thereof, have been prepared as inhibitors of the binding of adhesive proteins to the surface of different types of cell and accordingly influence cell-cell and cell-matrix interactions (no data). Thus, reaction of N-methylisatoic acid anhydride with glycine Et ester hydrochloride, followed by treatment with bromoacetyl bromide and subsequent nitration, catalytic hydrogenation, reaction with benzylisocyanate, coupling with (R,S)-3-amino-3-phenylpropanoic acid Et ester and subsequent ester hydrolysis, afforded benzodiazepinedione II. They can be used in the form of pharmaceutical prepns. for the treatment or prevention of neoplasms, tumor metastasis, tumor growth, osteoporosis, Paget's disease, diabetic retinopathy, macular degeneration, restenosis following vascular intervention, psoriasis, arthritis, fibrosis, kidney failure as well as infection caused by viruses, bacteria or fungi.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:824520 CAPLUS
DOCUMENT NUMBER: 134:2341
TITLE: Using markers for the identification of breast cancer and precancer from breast duct samples
INVENTOR(S): Hung, David T.
PATENT ASSIGNEE(S): Pro Duct Health, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000070349	A1	20001123	WO 2000-US13713	20000517 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
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US 6638727	B1	20031028	US 1999-313463	19990517 <--
US 20030022161	A1	20030130	US 2000-502404	20000210 <--
US 6642010	B2	20031104		
WO 2000051666	A1	20000908	WO 2000-US5142	20000229 <--
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1165160 A1 20020102 EP 2000-913661 20000229 <--
EP 1165160 B1 20070808
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 2003535617 T 20031202 JP 2000-602328 20000229 <--
AT 369157 T 20070815 AT 2000-913661 20000229
EP 1818017 A2 20070815 EP 2007-9685 20000229
EP 1818017 A3 20070829
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
CA 2372783 A1 20001123 CA 2000-2372783 20000517 <--
AU 2000054414 A 20001205 AU 2000-54414 20000517 <--
AU 775496 B2 20040805
EP 1179184 A1 20020213 EP 2000-939309 20000517 <--
EP 1179184 B1 20070711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY
JP 2002544521 T 20021224 JP 2000-618733 20000517 <--
US 20020110609 A1 20020815 US 2001-827371 20010406 <--
WO 2002080985 A1 20021017 WO 2002-US8232 20020403 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AU 2002258542 A1 20021021 AU 2002-258542 20020403 <--
EP 1372738 A1 20040102 EP 2002-728494 20020403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004532216 T 20041021 JP 2002-579023 20020403
AU 2008202312 A1 20080619 AU 2008-202312 20080526

PRIORITY APPLN. INFO.:

US 1999-313463	A	19990517
US 1999-166100P	P	19991117
US 1999-473510	A	19991228
US 2000-502404	A	20000210
US 1998-114048P	P	19981228
US 1999-117281P	P	19990126
US 1999-122076P	P	19990301
US 1999-134613P	P	19990518
US 1999-143359P	P	19990712
US 1999-143476P	P	19990712
US 1999-170997P	P	19991214
EP 2000-913661	A3	20000229
WO 2000-US5142	W	20000229
WO 2000-US13713	W	20000517
US 2001-827371	A	20010406
AU 2002-237838	A3	20020116
WO 2002-US1142	W	20020116
WO 2002-US8232	W	20020403

AB The invention concerns a method of screening women for breast

cancer or precancer. A method is provided that uses a patient's ductal fluid sample and examines the sample to determine the presence for marker(s) that can identify a patient's risk for breast cancer. The authors provide an extensive listing of the potential markers that may be used.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:795994 CAPLUS
DOCUMENT NUMBER: 132:31744
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Ltd., UK
SOURCE: PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964627	A2	19991216	WO 1999-GB1780	19990604 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
GB 1998-12099	A	19980606
GB 1998-13291	A	19980620
GB 1998-13611	A	19980624
GB 1998-13835	A	19980627
GB 1998-14110	A	19980701
GB 1998-14580	A	19980707
GB 1998-15438	A	19980716
GB 1998-15574	A	19980718
GB 1998-15576	A	19980718
GB 1998-16085	A	19980724
GB 1998-16086	A	19980724
GB 1998-16921	A	19980805
GB 1998-17097	A	19980807
GB 1998-17200	A	19980808
GB 1998-17632	A	19980814
GB 1998-17943	A	19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the number of genes and their configurations (mutations and polymorphisms) needed to be identified

in order to provide critical clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic" profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L34 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:795993 CAPLUS
DOCUMENT NUMBER: 132:31743
TITLE: Gene probes used for genetic profiling in healthcare screening and planning
INVENTOR(S): Roberts, Gareth Wyn
PATENT ASSIGNEE(S): Genostic Pharma Limited, UK
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9964626	A2	19991216	WO 1999-GB1779		19990604 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2330929	A1	19991216	CA 1999-2330929		19990604 <--
AU 9941586	A	19991230	AU 1999-41586		19990604 <--
AU 766544	B2	20031016			
AU 9941587	A	19991230	AU 1999-41587		19990604 <--
GB 2339200	A	20000119	GB 1999-12914		19990604 <--
GB 2339200	B	20010912			
EP 1084273	A1	20010321	EP 1999-925207		19990604 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2003528564	T	20030930	JP 2000-553616		19990604 <--
US 20030198970	A1	20031023	US 2002-206568		20020729 <--
PRIORITY APPLN. INFO.:			GB 1998-12098	A	19980606
			GB 1998-28289	A	19981223
			GB 1998-16086	A	19980724
			GB 1998-16921	A	19980805
			GB 1998-17097	A	19980807
			GB 1998-17200	A	19980808
			GB 1998-17632	A	19980814
			GB 1998-17943	A	19980819

	US 1999-325123	B1 19990603
	WO 1999-GB1779	W 19990604

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the number of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide critical clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L34 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	1999:717837 CAPLUS
DOCUMENT NUMBER:	131:314241
TITLE:	Stabilized protein crystals, formulations containing them and methods of making them
INVENTOR(S):	Margolin, Alexey L.; Khalaf, Nazer K.; St. Clair, Nancy L.; Rakestraw, Scott L.; Shenoy, Bhami C.
PATENT ASSIGNEE(S):	Altus Biologics Inc., USA
SOURCE:	PCT Int. Appl., 201 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9955310	A1	19991104	WO 1999-US9099	19990427	<--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2330476	A1	19991104	CA 1999-2330476	19990427	<--
AU 9937646	A	19991116	AU 1999-37646	19990427	<--
AU 757991	B2	20030313			
EP 1073421	A1	20010207	EP 1999-920064	19990427	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002512949	T	20020508	JP 2000-545510	19990427	<--
SG 121739	A1	20060526	SG 2002-6394	19990427	
US 20020045582	A1	20020418	US 1999-374132	19990810	<--
US 6541606	B2	20030401			
ZA 2000006023	A	20011113	ZA 2000-6023	20001026	<--
IN 2000KN00530	A	20050923	IN 2000-KN530	20001120	
US 20030175239	A1	20030918	US 2003-383266	20030305	<--
US 7351798	B2	20080401			

PRIORITY APPLN. INFO.:	US 1997-70274P	T0 19971231

US 1998-83148P	P	19980427
US 1998-224475	A2	19981231
WO 1999-US9099	W	19990427
US 1999-374132	A1	19990810

AB Methods are provided for the stabilization, storage, and delivery of biol. active macromols., such as proteins, peptides and nucleic acids. Methods are provided for the crystallization of proteins and nucleic acids and for the preparation of stabilized protein or nucleic acid crystals for use in dry or slurry formulations in pharmaceutical and veterinary formulations, diagnostics, cosmetics, food, and agricultural feeds. The crystals are stabilized by addition of excipients such as carbohydrates or by encapsulating them in a polymeric carrier. Methods are presented for encapsulating proteins, glycoproteins, enzymes, antibodies, hormones, and peptide crystals or crystal formulations into compns. for biol. delivery to humans and animals. Thus, lipase from Candida rugosa was dissolved in distilled water, treated with celite, adjusted to pH 4.8 with AcOH, filtered, ultrafiltered to remove proteins of <30 kDa mol. weight, and crystallization was initiated by addition of 2-methyl-2,4-pentanediol. Sucrose was added to the mother liquor to a concentration of 10%, and the crystals were separated by centrifugation, suspended in EtOH, and air dried at room temperature Alternatively, the lipase crystals were crosslinked and encapsulated in lactic acid/glycolic acid copolymer; the microspheres formed were 90 μm in diameter

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:572040 CAPLUS
DOCUMENT NUMBER: 131:185245
TITLE: Preparation of N-hydroxybenzamidine derivatives of β-amino-L-alanine with potent affinity to receptor of cell adhesion activating protein
INVENTOR(S): Miyauchi, Hiroshi; Tanaka, Masashi; Ohashi, Naohito
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 25 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
JP 11240862	A	19990907	JP 1998-241054		19980811	<--
PRIORITY APPLN. INFO.:			JP 1997-367411	A	19971224	

OTHER SOURCE(S): MARPAT 131:185245

AB 3-[[[4-(Hydroxyamidino)phenoxy- or benzoylamino]alkanoyl]amino]-2-aminopropanoic acid derivs. [I; R1 = CONR7. O, NR8, S(O)m, NR9CO; R7 - R9 = H, C1-6 alkyl; m = 0,1,2; R2 = H, (un)substituted C1-6 alkyl, cycloalkyl, C2-6 alkenyl or alkynyl, aryl, or heterocyclyl; R3 = (un)substituted C1-6 alkyl, cycloalkyl, C2-6 alkenyl or alkynyl, aryl, or heterocyclyl; R4, R5, R6 = H, C1-6 alkoxycarbonyl; n = 2,3] or pharmaceutically acceptable salts thereof are prepared These compds. selectively and strongly interacts with receptors of cell adhesion activating proteins such as fibrinogen and fibronectin and are excellent in oral absorbability and are useful as blood platelet aggregation inhibitors, cancer metastasis inhibitors, wound healing agents, and bone absorption inhibitors. Thus, hydroxylamine hydrochloride and NaOMe were added to a solution of 3-methylbutyl (2S)-3-(3-(4-

cyanobenzoylamino)propanoylamino)-2-((4-ethylbenzenesulfonyl)amino)propano
ate in MeOH and stirred at room temperature for 15 h, followed by
saponification and
acidification with aqueous HCl to give the title compound (II). When
administered p.o., II at 1 mg/kg ex vivo exhibited blood platelet
aggregation in guinea pigs by 72.3, 83.2, 90.0, and 77.6% after 0.5, 1, 2,
and 4 h, resp.

L34 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:33365 CAPLUS
DOCUMENT NUMBER: 126:73213
ORIGINAL REFERENCE NO.: 126:14141a,14144a
TITLE: Competitive inhibition of pulmonary metastasis of hamster osteosarcoma by peptides containing the core sequence of cell-adhesive molecules
AUTHOR(S): Nakagawa, Takuzo; Akamatsu, Noriya
CORPORATE SOURCE: Department Orthopaedic Surgery, Yamanashi Medical University, Tamaho, 409-38, Japan
SOURCE: Yamanashi Ika Daigaku Zasshi (1996), 11(3), 37-47
CODEN: YIDZE8; ISSN: 0912-0025
PUBLISHER: Yamanashi Ika Daigaku Igakkai
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tumor invasion and metastasis may occur due to altered mechanisms of adhesion of cells to the extracellular matrix. The RGD sequence (Arg-Gly-Asp) commonly exists in some adhesion-related mols. including fibronectin, vitronectin, fibrinogen and von Willebrand factor. It is believed that synthetic peptides containing the RGD core sequence are able to inhibit the formation of tumor colonies in the lungs. To control pulmonary metastases, the author investigated the antimetastatic activity of the RGD core sequence in the cell-binding fragment of fibronectin in the metastatic process of hamster osteosarcoma. Primary and metastatic tumor cells from hamster osteosarcoma were analyzed by cytofluorometry to investigate the populations of fibronectin receptors on the surface of each cell type. Inhibitors containing the characteristic sequence in fibronectin reduced metastatic colonization in the lung lesions. Fibronectin receptors on the cells from lung metastatic lesions increased compared to those from primary lesions. These results indicate that the mechanism of metastasis is related to the interaction between fibronectin and the fibronectin receptor. It also suggests that inhibitors which contain the RGD core sequence decrease pulmonary metastatic colonization through by interfering with the cellular adhesive process.

L34 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:881315 CAPLUS
DOCUMENT NUMBER: 123:286740
ORIGINAL REFERENCE NO.: 123:51407a,51410a
TITLE: Preparation of peptides containing 2,3-diaminopropionic acid derivatives having selective affinity to cell adhesion activating protein receptors
INVENTOR(S): Ikeda, Yoshiharu; Ueki, Yasuyuki; Kishimoto, Hisakazu; Nishihara, Toshio; Kamikawa, Yumiko
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 231 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9511228	A1	19950427	WO 1994-JP1700	19941011 <--
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2174516	A1	19950427	CA 1994-2174516	19941011 <--
AU 9478627	A	19950508	AU 1994-78627	19941011 <--
EP 725059	A1	19960807	EP 1994-929640	19941011 <--
EP 725059	B1	20010117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
CN 1138322	A	19961218	CN 1994-194559	19941011 <--
CN 1076345	C	20011219		
AT 198739	T	20010215	AT 1994-929640	19941011 <--
US 5707994	A	19980113	US 1996-633800	19960419 <--
US 6048854	A	20000411	US 1997-937901	19970925 <--

PRIORITY APPLN. INFO.: JP 1993-286091 A 19931019
JP 1993-350177 A 19931228
WO 1994-JP1700 W 19941011

OTHER SOURCE(S): MARPAT 123:286740

AB The title peptides X-R5-A3-R4-A2-R3-A1-NHCH2CH(CO2R1)NHSO2R2 [R1 = H, (un)substituted alkyl, cycloalkyl, alkenyl, alkynyl, aryl, or heterocyclyl; R2 = group listed in R1 except H; A1 = CO, CO-A4; wherein A4 = α- or β-amino acid residue, derivative residue thereof, or peptide residue comprising 2 or 3 of these amino acid residues; A2, A3 = single bond, NR6, O, S(O)n, CONR7, NR7CO, CO-A5-NR8, NR8-A5-CO, bivalent monocyclic hydrocarbon or heterocyclic ring; wherein R6, R7, R8 = H, alkyl; n = 0,1; A5 = α- or β-amino acid residue, derivative residue thereof, or dipeptide residue comprising 2 of these amino acid residues; R3, R4 , R5 = single bond, alkylene, alkenylene, or alkynylene each optionally substituted by 1-4 of OH, oxo, halo, aryl, or cycloalkyl; X = Q, Q1, or Q2, when number of atoms constituting the bivalent R5-A3-R4-A2-R3-A1 group is 6-11, 4-9, and 4-9, resp.; Y1, Y2, Y3 = CH, N; V1, V2, V6, V7 (substituent on a C atom) = H, alkyl; V3, V4 = H, (un)substituted alkyl, cycloalkyl, NH2, acylamino, alkoxycarbonyl, arylalkyloxycarbonyl; V5 = imino or O; m = 2-3] or pharmaceutically acceptable salts thereof are prepared These compds. are useful as platelet aggregation inhibitors, cancer metastasis inhibitors, wound remedies, or bone resorption inhibitors. Thus, Z-Asn-OH was treated with [bis(trifluoroacetyl)iodo]benzene in aqueous DMF for 15 min and with pyridine for 4 h to give (2S)-3-amino-2-benzyloxycarbonylaminopropanoic acid, which was acylated by (Boc)2O in aqueous 1,4-dioxane, esterified with MeOH by using 4-dimethylaminopyridine and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in CH2Cl2, treated with MeSO3H in MeCN at 20° to room temperature to give, and condensed with N-tert-butoxylcarbonyl-β-alanine by using HOBT.H2O and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride at room temperature to give (2S)-Boc-NHCH2CH2CONHCH2CH(NHR)CO2Me (I; R = CO2CH2Ph). The latter compound was hydrogenolyzed over 10% Pd-C in AcOEt-EtOH and condensed with PhSO2Cl in CH2Cl2 containing Et3N to give I (R = SO2Ph) which was treated with MeSO3H in MeCN, neutralized with a DMF solution of Et3N, and condensed with N-tert-butoxylcarbonyl-4-amidinobenzoic acid by using HOBT.H2O and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride to give, after treatment with CF3CO2H under ice-cooling, a

title peptide (II.CF3CO2H). II.CF3CO2H in vitro showed IC50 of 4.6 + 10-9, 2.0 + 10-7, and 1.0 + 10-6 M for inhibiting the binding of blood platelet to cell adhesion proteins such as human fibrinogen, human fibronectin, and human vitronectin, resp. It was administered to guinea pigs at 0.1 mg/kg p.o. and the blood samples of the animals were taken after 0.5-6 h and treated with ADP to show 100% inhibition of the ADP-induced blood platelet coagulation.

L34 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:508004 CAPLUS
DOCUMENT NUMBER: 122:266008
ORIGINAL REFERENCE NO.: 122:48588h,48589a
TITLE: Preparation of novel dipiperidine derivative with selective affinity to receptor of cell adhesion protein
INVENTOR(S): Ikeda, Yoshiharu; Ueki, Yasuyuki; Nishihara, Toshio; Kamikawa, Yumiko
PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9501336	A1	19950112	WO 1994-JP908	19940606 <--
W: CA, CN, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2166075	A1	19950112	CA 1994-2166075	19940606 <--
EP 706999	A1	19960417	EP 1994-917158	19940606 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
US 5607948	A	19970304	US 1995-578697	19951228 <--
PRIORITY APPLN. INFO.:			JP 1993-189120 A	19930630
			WO 1994-JP908 W	19940606

OTHER SOURCE(S): MARPAT 122:266008
AB A novel dipiperidine derivative represented by general formula {I; R1 = H, lower alkyl; Y = a single bond, O; n = 1, 2 or 3; W = CH2, O; R2 = H or a carboxyl-modifying group eliminable in vivo; X1, X3 = H, lower alkyl; X2 = H, lower alkyl, aryl, CHX4OX5 (wherein X4 = H, Me; X5 = H, HO-modifying group), CH2CH2OX5, C(X4)2SX6 (wherein X6 = H or thiol-modifying group), CH2CH2S(O)mMe (wherein m = 0, 1, 2), (CH2)pCO2X7 (wherein p = 1,2; X7 = H, HO2C-modifying group), (CH2)pCONHX8 (wherein X8 = H, amide-modifying group), (CH2)qNHX9 (wherein q = 3,4; X9 = H, H2N-modifying group), (CH2)qNHC(:NH)NHX10 (wherein X10 = H, guanidino-modifying group) , (CH2)rX11 [wherein r = 1,2; X11 = halo, cycloalkyl, (un)substituted aryl or heterocyclyl]; or X1 and X2 forms trimethylene or tetramethylene; or X2 and X3 forms pentamethylene} or a pharmacol. acceptable salt thereof is prepared This dipiperidine derivative of an amino acid I show selective affinity to receptors of cell adhesion proteins such as fibronectin, laminin, and vitronectin and is useful as a novel platelet aggregation inhibitor, cancer metastasis inhibitor, wound remedy or bone resorption inhibitor. Thus, Z-Tyr(Me)-OH was condensed with tert-Bu 4-piperidyloxyacetate hydrochloride by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride hydrochloride, hydroxybenzotriazole, and Et3N in DMF to give tyrosine derivative (II; R = benzyloxycarbonyl; R3 = tert-butyl). The latter compound was hydrogenolyzed over 10% Pd-C in MeOH to give II (R = H, R3 = tert-butyl) which was similarly condensed with 1-benzyloxycarbonyl-4-piperidyloxyacetic acid (preparation given) to give, after deprotection by hydrogenolysis over 10% Pd-C

and treatment with CF3CO2H, II (R = Q, R3 = H) (III). III showed IC50 of 48 nM for inhibiting the ADP-induced aggregation of human platelet rich plasma and 0.45, 67, and >100 μM for inhibiting the binding of fibrinogen, fibronectin, and collagen to blood platelet, resp.

L34 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:701332 CAPLUS
DOCUMENT NUMBER: 121:301332
ORIGINAL REFERENCE NO.: 121:55181a,55184a
TITLE: Preparation of heterocyclylpeptides as drugs.
INVENTOR(S): Klingler, Otmar; Breipohl, Gerhard; Zoller, Gerhard; Jablonka, Bernd; Just, Melitta; Knolle, Jochen; Koenig, Wolfgang
PATENT ASSIGNEE(S): Cassella AG, Germany
SOURCE: Ger. Offen.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4308034	A1	19940915	DE 1993-4308034	19930313 <--
CA 2155842	A1	19940929	CA 1994-2155842	19940219 <--
WO 9421607	A1	19940929	WO 1994-EP481	19940219 <--
W: AU, CA, HU, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9461423	A	19941011	AU 1994-61423	19940219 <--
AU 678438	B2	19970529		
EP 688315	A1	19951227	EP 1994-908350	19940219 <--
EP 688315	B1	19990506		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
HU 72756	A2	19960528	HU 1995-2660	19940219 <--
JP 08509209	T	19961001	JP 1994-520559	19940219 <--
JP 3547745	B2	20040728		
AT 179698	T	19990515	AT 1994-908350	19940219 <--
ES 2133543	T3	19990916	ES 1994-908350	19940219 <--
ZA 9401714	A	19941005	ZA 1994-1714	19940311 <--
IL 108943	A	20010430	IL 1994-108943	19940311 <--
US 5658935	A	19970819	US 1996-513897	19960117 <--

PRIORITY APPLN. INFO.: DE 1993-4308034 A 19930313
WO 1994-EP481 W 19940219

OTHER SOURCE(S): MARPAT 121:301332
AB Title compds. [I; Z1 = CO, CS; Z2 = CO, CS, CH2; Y = (CH2)mCO, CHR5CO, C6H4CO; m = 1-4; r = 0-3; A = CHR1, NR1, X1C6H4CH:C; B = CH2, O; W = COW1, tetrazolyl, SO3H, SO2NHR9; X1 = (CH2)qNHX, (CH2)pC(:NX)NH2; p, q = 0-3; W1 = OH, alkoxy, (substituted) arylalkoxy, aryloxy, amino; R = H, alkyl; R1 = Q1, (CH2)nNHX, etc.; n = 1-6; t = 0-2; X = H, alkyl, alkylcarbonyl, alkoxycarbonyl, (substituted) arylcarbonyl, aryloxycarbonyl, etc.; R2 = H, (substituted) alkyl, Ph; R3 = H, CO2R4, CONMeR4, CONHR4; R4 = H, (substituted) alkyl; R5 = amino acid side chain; R9 = H, aminocarbonyl, alkyl, cycloalkyl; with provisos], were prepared as inhibitors of thrombocyte aggregation, tumor cell metastasis, and osteoclast binding to bone surfaces (no data). I inhibit binding of fibrinogen, fibronectin, and von Willebrand factor to integrin receptors (no data). Thus, [3-[4-(aminoiminomethyl)benzyl]-2,5-dioxopyrrolidin-1-yl]acetylaspartylphenylglycine was prepared via coupling of [3-[4-(aminoiminomethyl)benzyl]-2,5-dioxopyrrolidin-1-yl]acetic acid hydrochloride (preparation starting from tri-Et 1,1,2-ethanetricarboxylate and 4-bromomethylbenzonitrile given) with H-Asp(OtBu)-Phg-OtBu (Phg =

phenylglycyl) using TOTU/N-ethylmorpholine in DMF.

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L1             STRUCTURE UPLOADED
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L3           0 S L1 SSS FULL
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L5             STRUCTURE UPLOADED
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               S L5

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L10            STRUCTURE UPLOADED
L11            QUE L10 AND L9
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     FILE 'CAPLUS' ENTERED AT 09:43:05 ON 12 SEP 2008
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L15       5292 S L14 AND INHIBITORS
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L17       1901 S L16 AND ALPHA-IIB
L18       1264 S L17 AND PY<=2003
L19          4 S L18 AND SPIRO

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     FILE 'CAPLUS' ENTERED AT 10:14:04 ON 12 SEP 2008
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L23          5 S L22 AND BONE
L24          2 S L22 AND "TUMOR CELL"
L25        367 S L18 AND FIBRINOGEN
L26          0 S L25 AND BOBE
L27          6 S L25 AND BONE
L28          2 S L25 AND SPIRO
L29      36894 S FIBRINOGEN
L30       2769 S L29 AND RECEPTORS
L31        635 S L30 AND INHIBITORS
L32        174 S L31 AND (TUMOR OR CANCER)
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L34         16 S L33 AND PY<=2003
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